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Case Report Open access

Hypertensive Emergency in Adolescent with Systemic Lupus Erythematosus at Onset: A Case Report

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Abstract

The severity of Systemic lupus erythematosus (SLE) at onset represents the most important biomarker of disease outcome and of treatment response in paediatric patients. Kidney disease, chronic systemic inflammation and steroid toxicity could cause hypertension development.

Thirteen year old child presenting with serositis, hemolytic anemia, leucopenia, thrombocytopenia and lupus nephritis was treated according to Euro Lupus Protocol. A progressive deterioration of kidney function was observed during the treatment with increased blood pressure for about a month after the beginning of the treatment. The antihypertensive therapy established by the Italian society of pediatrics (SIP) and consisting of diuretic therapy (Furosemide 1 mg/Kg/die) and angiotensin-converting-enzyme (ACE) inhibitor therapy (Enalapril 0.06 mg/Kg/die) was initiated. Persisting hypertensive peaks, calcium antagonist therapy (Amlodipina 5 mg/die) and α2 adrenergic therapy (Clonidina one plaster/2.5 mg/week) were added. After gaining control of the hypertensive peaks, the antihypertensive treatment was gradually reduced.

There are no treatment protocols for the management of hypertension associated with SLE in children in the literature. In our case the early treatment with the SIP protocol determined reduction in urinary protein levels and avoided acute organ damage related to hypertension peaks.

Keywords: Hypertension; Lupus nephritis; Systemic lupus erythematosus; Aolescent; Management

Abbreviations:

SLE: Systemic Lupus Erythematosus; SIP: Italian Society of Pediatrics; ACE: Converting-enzyme; EBV: anti-Epstein Barr Virus; ANA: Antinuclear Antibody; nDNA: Double Stranded DNA; ACR: American College of Rheumatology; CYC: Cyclophosphamide; ARB: Angiotensin II Receptor Antagonist Blockers; LN: Lupus Nephritis; CKD: Chronic Kidney Disease

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic involvement with a broad spectrum of clinical and laboratory manifestations, predominantly affecting young individuals [1]. The diagnosis is made when four of the eleven criteria established by the American College of Rheumatology are satisfied [2].

The severity of SLE at presentation represents the most important biomarker of the disease outcome and of the treatment response in paediatric patients. In particular, an onset with nephrotic syndrome and presence of anticardiolipin antibodies and lupus anticoagulants are often related to a more serious outcome due to the risk of developing thromboembolic events [3]. Kidney disease, chronic systemic inflammation and steroid toxicity could cause hypertension development [4,5].

Case Report

We describe the case of a child aged thirteen years who was admitted to the emergency room of our hospital with fever and positivity for anti-Epstein Barr virus (EBV) antibodies. Before hospitalization the patient was treated with Clarithromycin, without benefit. The physical examination of organs and apparatus showed laterocervical adenopathy and splenomegaly and the laboratory examinations highlighted the association with thrombocytopenia and anemia. A chest X-ray was performed that showed "prominent bronchovascular markings", thus an antimicrobial treatment with ampicillin and sulbactam was started. Due to the worsening of thrombocytopenia, the patient was transferred to the pediatric oncohematology unit of our hospital where she was subjected to bone marrow aspiration to exclude blood cancer. The lymphocyte subset panel was suggestive of an autoimmune disorder, which was confirmed by positivity of the direct Coombs tests, antinuclear antibody (ANA) title (1/2560), anti-double stranded DNA (nDNA) antibodies title (1/40) and anticardiolipin antibodies. The laboratory tests showed also complement factor consumption. The Doppler echocardiography pointed out mitral valve insufficiency and a small pericardial effusion, while the abdominal ultrasound showed the presence of ascites. The rheumatological evaluation let to diagnose of SLE disease, according to the presence of four of the eleven diagnostic criteria established by the

American College of Rheumatology (ACR) (serositis, hemolytic anemia, leucopenia and thrombocytopenia) in association with the presence of the immunological criteria (positivity of ANA, anti-dsDNA, antiphospholipid antibodies, direct Coombs tests and complement factor consumption) [6]. After rheumatological evaluation, the child discovered to have SLE. Indeed, the patient was transferred to our pediatric department, where she started the treatment approved by the Euro Lupus Protocol, consisting of 3 daily pulses of 750 mg of methylprednisolone followed by 6 fortnightly Cyclophosphamide (CYC) pulses at a fixed dose of 500 mg and oral glucocorticoid therapy at an initial dosage of 0.5 mg/kg/day of Prednisolone. Later, according to Euro Lupus Protocol for critical patients (those with renal impairment or severe extra-renal disease), she received dosage of 1 mg/kg/day [7,8]. During the treatment, specifically until the third administration of the CYC, a progressive deterioration of the kidney function was observed; meanwhile increase in blood pressure values and enlargement of the pericardial effusion occurred. Therefore, the antihypertensive therapy established by the Italian Society of Pediatrics (SIP) was initiated [9,10] which consists of diuretic therapy (Furosemide 1 mg/Kg/die) and angiotensin converting enzyme (ACE) inhibitor therapy (Enalapril 0.06 mg/Kg/die). Persisting hypertensive peaks, calcium antagonist therapy (Amlodipina 5 mg/die) and α2 adrenergic therapy (Clonidina one plaster/2.5 mg/week) were added. Furthermore, to control pericardial effusion Acetylsalicylic Acid at the dose of 500 mg day was started and continued for seventeen days at a progressively decreasing dosage. After controlling the hypertensive peaks, the antihypertensive treatment was gradually reduced: firstly interrupting Clonidina plaster, then Amlodipina and finally diuretic therapy. As a gradual improvement of pericardial effusion was noted, the steroidal therapy was progressively reduced weekly in relation to the clinical progression, and treatment with Mycophenolate Mofetil was started at the dosage of 600 mg/m^2 twice a day [7]. This has led to good control of the disease, although low proteinuria persists (<1 gr/day). During the course of illness, because of anemia, the patient was subjected to two blood transfusions. Once the patient was clinically stable, a kidney biopsy was performed which showed "thrombotic microangiopathy and acute interstitial nephritis in association with membranous glomerulonephritis at an early stage". Therefore she takes an Angiotensin II receptor antagonist blockers (Losartan) (ARB) at the dosage of 25 mg/day and an ACE inhibitor (Enalapril) at the dosage of 10 mg/day as antihypertensives and practices an antithrombotic therapy with Aspirin at the dosage of 100 mg daily. She also performed the Dual-energy x-ray absorptiometry showed a feature of mild osteopenia (z score of -1.1).

Discussion

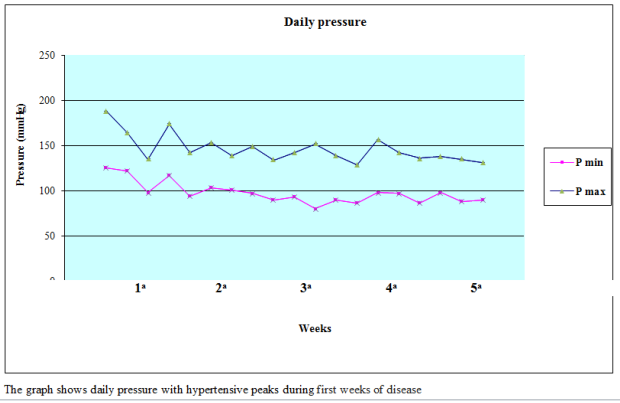
Lupus nephritis (LN) is an inflammatory condition of the kidney that encompasses various patterns of renal disease including glomerular and tubulointerstitial pathology [7]. The diagnosis meets the criteria of the ACR: persistent proteinuria >0.5 gr/die or higher to +3 by dipstick, and/or cellular casts including red cell, hemoglobin, granular, tubular or mixed. A review of the ACR criteria suggested that a spot urine creatinine/protein ratio >0.5 can be substituted with a 24 hour protein measurement and it is the major predictor of a poor prognosis in patients with SLE [2]. According to literature, the environmental triggering factors are heterogeneous, in our case probably the EBV infection was implicated in the pathogenesis [7]. Only in 15-20% of patients with SLE the diagnosis is made before 18 years of age; LN has been reported to be more prevalent in patients with early-onset SLE, than in those with late-onset [11-13]. In the literature, there is evidence that, even when treated with aggressive immunosuppression protocols, 30-50% of patients with class IV LN develop end-stage renal disease within the first 10 years of follow-up [14,15]. Furthermore among SLE patients, children receive more intensive drug therapy and suffer more damage, often related to steroid toxicity, then adults [16]. According to literature our patient showed almost immediately active and aggressive renal disease and despite immediately receiving steroid and aggressive immunosuppression protocols, developed a progressive deterioration of the kidney function. Meanwhile, an increase in blood pressure values and enlargement of the pericardial effusion occurred.

In SLE the immune cells, that form immune complexes and impair renal function, have been implicated in the pathogenesis of hypertension [4,5]. Moreover, the chronic inflammation damages the cholinergic anti-inflammatory pathway and decreases vagal nerve activity [17]. Previous studies in pediatric SLE patients report a frequency of hypertension and nephrotic syndrome at presentation ranging from 40-55% and 18-40% respectively [18-21]. Another study reported 71% of hypertension and 57% of nephrotic syndrome at presentation [3]. A study showed that SLE pediatric patients have higher rates of night-time systolic blood pressure compared to daytime, either isolated nocturnal hypertension with normal daytime blood pressure or in conjunction with daytime hypertension. Our patient had hypertensive peaks for about a month after the beginning of the treatment especially at night-time (Graph 1). There was no statistically significant association between laboratory measures (complement, ANA, anti-dsDNA antibodies, etc.) and nocturnal hypertension [22]. This is a severe condition that needs immediate antihypertensive therapy, especially in the presence of organ damage or renal disease, while avoiding an abrupt slump of blood pressure. In the presence of renal disease without proteinuria, blood pressure must be <75°pc for gender, age and stature, while in the presence of renal disease with proteinuria, blood pressure must be <50°pc for gender, age and stature [9,10]. The lowest risk for chronic kidney disease (CKD) progression was found in patients whose systolic blood pressure was maintained in a range of 110–129 mmHg, especially in those individuals with proteinuria (1 g/days). Otherwise, an increase in relative risk for CKD progression at pressures above 130 mmHg has been noted [23]. The optimal blood pressure for all ages with CKD is 140/90 [24-26]. In our case the antihypertensive therapy was initiated according to the guidelines established by SIP. Once hypertensive peaks were controlled, the antihypertensive treatment was gradually reduced keeping ACE inhibitor and ARB.

In fact literature advises that all patients with proteinuria of more than or equal to 0.5 g in 24 h should receive renin-angiotensin system blockade [27]. ACE inhibitor therapy and ARB not only help maintain blood pressure lower than 130/80 mmHg, but also reduce proteinuria and may even prevent the development of biopsy-proven glomerulonephritis [28,29].

In the literature there are not treatment protocols for the management of hypertension associated with SLE in children. In our case using the SIP protocol for early hypertensive emergency treatment, a gradual reduction in blood pressure was achieved which resulted in improved outcomes of kidney disease. The particularity of this case report is that lupus nephritis onset occurred with hypertensive peaks before progressive deterioration of kidney function and SIP protocol, for early hypertensive emergency, is an effective treatment to control hypertensive peaks in children (Graph 1).

Further studies needed to manage SLE associated hypertension in children.



Graph 1: Daily pressure over a five-week period.

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