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ORIGINAL PAPER

Treatment-Associated Side Effects in Patients with Steroid-Dependent Nephrotic Syndrome

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ABSTRACT

Introduction: *Nephrotic syndrome is one of the most extensively studied pediatric diseases for a nephrologist. Treatment for patients suffering from it has greatly improved the prognosis and reduced the mortality rate to 3% or less. Steroid medication is the first line, but non-steroid immunosuppressive drugs are useful in limiting steroid side effects and maintaining long-term remission.*

Objective: *The aim of the study is to choose the best treatment for each patient in order to minimize long-term effects of corticosteroid therapy, taking into account the child's age, gender and other factors to optimize the quality of life.*

Materials and methods: *This is a retrospective study of pediatric patients older than one year and younger than 18 years of age diagnosed with idiopathic corticosteroid nephrotic syndrome. Study participants were treated in the Department of Pediatric Nephrology of "M. S. Curie" Emergency Clinical Hospital for Children, Bucharest, Romania, between January 2013 and December 2020. Thirty-seven subjects with steroid-dependent nephrotic syndrome from a total of 125 patients diagnosed with nephrotic syndrome were included in the present study. All study participants underwent clinical examination and laboratory tests and were regularly monitored.*

Results and discussion: *Long-term corticosteroid therapy can lead to unwanted complications such as hypertension, short stature, behavior disturbances, or osteopenia. To minimize certain side effects, a second line steroid-sparing agents can be used due to their ability to induce complete remission and maintain it in patients with steroid-dependent nephrotic syndrome.*

Conclusions: *Our study describes the most frequent side effects encountered in the Department of Nephrology in patients with steroid-dependent nephrotic syndrome. The purpose was to emphasize that pediatric patients' quality of life depends on limiting long-term corticosteroid treatment and preventing adverse reactions or complications.*

Keywords: corticosteroid-dependent nephrotic syndrome, steroids, non-immunosuppressive therapy, side effects.

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INTRODUCTION

Nephrotic syndrome (NS) is one of the most studied kidney diseases among pediatric patients, with a good prognosis in our days and a dramatic decline in the mortality rate (3% or less) (1). It is an idiopathic condition characterized by range nephrotic proteinuria (urine protein to creatinine ratio ≥200 mg/mmol, or 3+ protein on urine dipstick), hypoalbuminemia (serum albumin ≤3 g/dL), edema and hyperlipidemia (2-4).

Childhood nephrotic syndrome responds to steroid therapy, but 40-50% of patients suffering from it have either frequent relapses or steroid-dependency (5). Based on the response to corticosteroid therapy, NS has been classified as steroid-sensitive nephrotic syndrome (SSNS), steroid-dependent nephrotic syndrome (SDNS) and steroid-resistant nephrotic syndrome (SRNS).

Steroid-sensitive nephrotic syndrome appears when the patient obtains complete remission in the first 28 days after starting the steroid therapy. Steroid-dependent nephrotic syndrome is defined by two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy. Initial non-responder or steroid-resistant is when the patient fails to achieve complete remission after eight weeks of steroid therapy (3, 6).

The use of corticosteroid therapy represents a major breakthrough in pediatric nephrology, being the first line of treatment. We know the biological effects of glucocorticoids in every cell and system of the body. They affect carbohydrate metabolism, blood pressure and vascular trophicity, psychic mood and behavior, muscle and skin trophicity, weight, immunity, bone growth and mineralization (7). In the kidney, sodium reabsorption is affected by the concentration of glucocorticoid and leads to hypertension.

According to the KDIGO guidelines, glucocorticoids should be given daily (60 mg/m^2/day) for the first four weeks, followed by 40 mg/m^2 on alternate days for eight to 20 weeks, to reduce the steroid side effects.

Second line steroid-sparing agents include levamisole, mycophenolate mofetil (MMF), calcineurin inhibitors (cyclosporine, tacrolimus), alkylating agents (cyclophosphamide, chlorambucil). Optimal agent should maintain long-term remission and reduce steroid dosing and toxicity, with limited side effects (8).

Study objectives

The aim of the current study is to observe and evaluate the side effects of corticosteroid therapy and the second line immunosuppressive agents in order to improve patients' quality of life and maintain long-term remission. ❑

MATERIALS AND METHODS

We performed a retrospective study of pediatric patients older than one year and younger than 18 years of age who were diagnosed with idiopathic steroid-dependent NS (defined as two consecutive relapses while tapering corticosteroid therapy or within 14 days of stopping steroids) and received steroid treatment with or without second-line steroid-sparing agents. Relapse was defined as nephrotic range proteinuria as assessed by uPCR ≥2 000 mg/g or ≥3+ protein on urine dipstick for three consecutive days (3).

Patients were treated in the Department of Pediatric Nephrology of "M. S. Curie" Emergency Clinical Hospital for Children, Bucharest, Romania, between January 2013 and December 2020.

Thirty-seven subjects with SDNS from a total of 125 patients diagnosed with NS were included in the present study.

Data were collected from the medical records and included age, gender, corticosteroid therapy, signs of steroid toxicity (statural growth impairment, cataracts, excessive weight gain, cushingoid features, behavior disturbances, hypertension, gastrointestinal effects, hematologic effects), second-line steroid-sparing agent (levamisole, mycophenolate mofetil, cyclosporine, cyclophosphamide) efficacy and side effects.

Side effects of using second-line immunosuppressive agent were monitored depending on the type of medication that has been administered.

Levamisole, which stimulates the immune system, is the least toxic agent but can lead to hematologic abnormalities (neutropenia) as a side effect (9-11).

Mycophenolate mofetil inhibits T- and B-cell proliferation and is not nephrotoxic, but can have side effects which include abdominal pain,

diarrhea and hematological abnormalities and it can be teratogenic (12, 14).

Calcineurin inhibitors (CNIs) such as cyclosporine blocks T-cell activation and is nephrotoxic. In patients using cyclosporine we regularly monitor the serum creatinine level to prevent kidney function impairment. After we achieve remission, the dose is slowly reduced to < 5 mg/kg/day to reduce nephrotoxicity (15).

Alkylating agents such as cyclophosphamide can induce longer remissions than prednisone alone in SDNS. Adverse effects are severe due to depletion of immune-competent cells. Complications associated with these drugs include leucopenia, neutropenia, hemorrhagic cystitis, gonadal toxicity (high doses). It has been observed that iv cyclophosphamide (one dose/month for six months) was more effective in maintaining remission than oral cyclophosphamide for 8 to 12 weeks (16).

Criteria for choosing the second line stero id-sparing agent were based on the possibilities of our clinic and, in some cases, on patient's preference. ❑

RESULTS

A total of 125 patients were included in the study but only 37 of them had SDNS, among which 12 (32%) were females and 25 (68%) males. Subjects' age range was between one year and 12 years, most of them being aged 1–3 (Figure 1).

The diagnosis of SDNS was established as two consecutive relapses while tapering corticosteroid therapy or within 14 days of stopping steroid therapy. Most of our patients presented two consecutive relapses. All patients received pulse therapy with methylprednisolone either three or six doses. Eighteen patients maintained remission after treatment with oral prednisone and dose-tapering. After reaching the dose of 5-10 mg/day (< 0,75 mg/kg) on alternate days (13), this dose was maintained for six to 12 months, with no side effects or relapses. Two patients from this group were not compliant to treatment because they had a poor socio-economic status, missed appointment to the doctor, or were given prolonged high-dose treatment with prednisone. The remaining 19 subjects received second-line steroid-sparing agents, of which 13 patients needed only one drug, and six, a second non-steroid immunosuppressive drug after ending the first drug and relapsing after a short or longer time of remission. The following drugs were used: cyclosporine, levamisole, mycophenolate mofetil, cyclophosphamide.

Non-steroid immunosuppressive treatment was given for a period of six month to two years, depending on the drug, if no side effects were established.

Among the steroid-sparing agents, cyclosporine and cyclophosphamide were used to the greatest extent – six (32%) and five (26%) patients, respectively – and levamisole and mycophenolate mofetil to a lesser extent (Figure 2). In most cases, remission was achieved with one immunosuppressive drug, but six patients needed a second steroid-sparing agent to regain and maintain remission.

The choice of starting second-line immunosuppressive therapy was determined by the signs of steroid toxicity, which included statural growth impairment, excessive weight gain, cushingoid features, behavior disturbances (hyperactivity, mood disorders), hypertension, and hematological effects (leukocytosis and neutrophilia) (Figure 3).

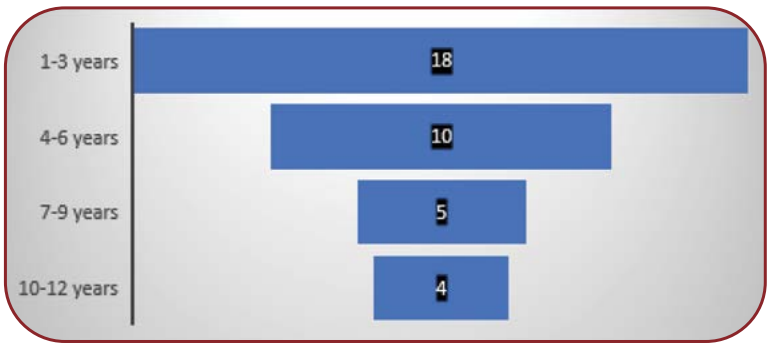

FIGURE 1. Age distribution for patients with steroid-dependent nephrotic syndrome (SDNS)

Most of the study participants presented with cushingoid featured, followed by hypertension or leukocytosis and neutrophilia.

Following the side effects of second-line non-steroid immunosuppressive therapy, no major complications were observed. Most of the patients presented with transient mild leucopenia or mild neutropenia (never values that forced the discontinuation of treatment), transient abdominal pain or nausea.

Patients who started treatment with cyclophosphamide received 500 mg/m^2/dose once monthly for six months. Before every dose, they were investigated for hematological, electrolytes abnormalities and abdominal ultrasound in addition to specific tests for NS.

Also for other immunosuppressive agents, including levamisole, cyclosporine, MMF, patients were periodically evaluated to prevent possible and complicated side effects. In two patients who received cyclosporine after started with 4-5 mg/kg/day in two divided doses, we had to reduce the dose gradually due to the elevated serum creatinine level. In these cases, remission was maintained for more than one year when we lowered the dose of cyclosporine.

There were six particular patients who ended up taking a second non-steroid immunosuppressive medication. In our study, after we achieved remission with the first steroid-sparing agent, some patients relapsed and needed a second drug: one patient after three months, two patients after six months, two patients after one year and one patient after two years.

During corticosteroid therapy or non-steroid immunosuppressive medications, patients also received angiotensin-converting enzyme (ACE) inhibitors, which are known to decrease proteinuria. ❑

DISCUSSION

Steroid therapy is still the answer for obtaining remission in patients with NS (17, 18). The negative part of steroid therapy is represented by its relative efficiency to prevent relapses,

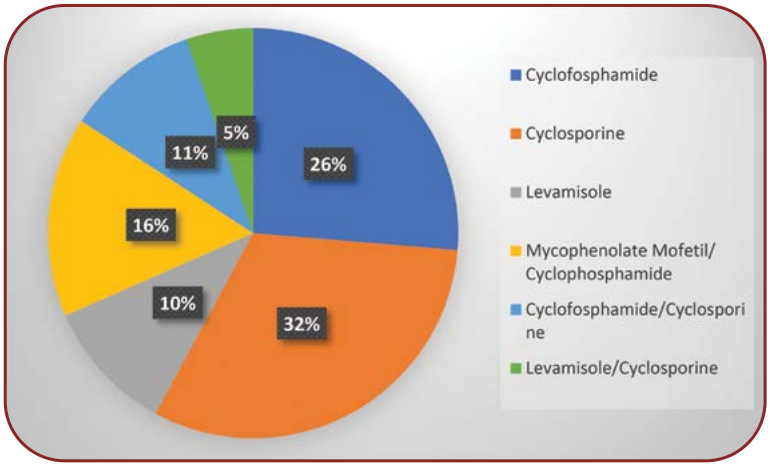

FIGURE 2. Second line steroid-sparing agents used in patients with steroid-dependent nephrotic syndrome (SDNS)

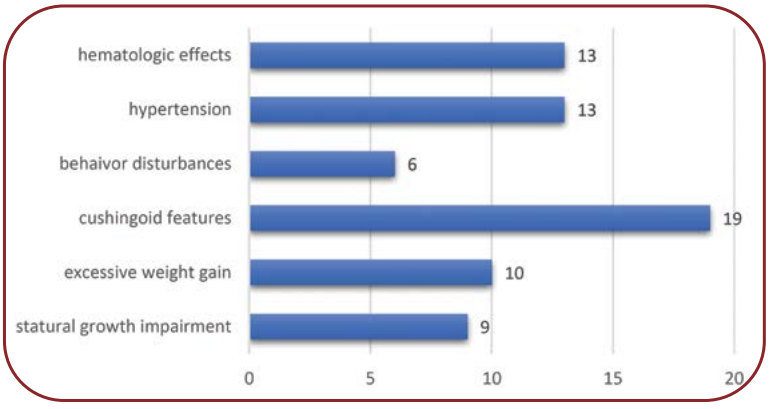

FIGURE 3. Complications related to corticosteroid therapy in nephrotic syndrome

long-term complications and poor compliance of patients with longer treatment duration (19-21).

Most of the patients enrolled in our study with a diagnosis of SDNS were small children aged between one year and three years (48%), and some of them had frequent relapses even under second-line steroid-sparing agents.

Eighteen patients only needed corticosteroid therapy. From this group, 10 patients responded to prednisone at a smaller dose of 1 mg/kg daily for a period of 7-10 days during relapses. The same effect was seen in a study in which Raja K. enrolled 50 patients (22).

According to other studies, maintaining a small dose of prednisone (<0,75 mg/kg) for a longer period of time during complete remission will not have side effects on children's growth or other complications specific for long-term use of high-dose steroid treatment. In our cases, when the patient was taking prednisone 5-10 mg/day on alternate days (23, 24), this dose was given for a period of six to 12 months, with no side effects or relapses.

In our study, the signs of steroid toxicity which were the most frequently seen included cushingoid features (19 cases), followed by hypertension (13 cases), hematologic abnormalities (13 cases), excessive weight gain (10 cases), behavior disturbances (six cases) and statural growth impairment (nine cases) (24). Cushingoid features seen in the study group included "moon" face, hirsutism associated with weight gain and short stature. Hypertension was defined as blood pressure >95th percentile for sex, height and age. Behavior disturbances included mood change, irritability, increased appetite.

All these complications caused by corticosteroid therapy affects patients' quality of life and could have a serious impact on their emotional health and social relationship in the future as adults (25).

As steroid-sparing medication, the second choice for most patients was either cyclosporine or cyclophosphamide. Side effects of this drug were minimum or transient and disappeared after finishing or lowering the dose. Cyclosporine had a surprising result on our patients. Four out of six patients who were taking cyclosporine maintained remission for two years and two subjects relapsed after six months, while for one patient it was nephrotoxic (26, 27).

Levamisole and MMF were not associated with side effects and were well tolerated by patients (28). In our study, MMF was not superior to levamisole and remission was maintained for approximately one year (29, 30). ❑

CONCLUSIONS

Since immunosuppressive therapies have been the answer to obtain a rapid remission, the lives of patients with nephrotic syndrome have changed. However, long-term use of these medications is associated with adverse effects and treatment-dependence or resistance among pediatric patients with NS.

Corticosteroid therapy remains the first line in childhood nephrotic syndrome. Some patients with SDNS maintain complete remission with prednisone monotherapy for a longer period of time even with a low dose.

Non-steroid immunosuppressive drugs give the possibility to limit the chronic use of prednisone, to prevent long-term toxicity, but keep in mind they also have side effects.

When choosing a medication, one should always think about the potential long-term side effects and their implications in patients' emotional and social life. ❑

Conflicts of interest: none declared.

Financial support: none declared.

Informed consent was obtained from all patients included in the study.

All procedures and experiments of this study are in accordance with both the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), and the national law.

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