Steroid Sensitive Nephrotic Syndrome and Steroid Toxicity: What to do Next?

A 10 year old boy presented to our hospital with nephrotic syndrome relapse and signs of steroid toxicity in the form of posterior capsular cataract, affection of linear growth and stage 2 hypertension, in addition to steroid induced adiposity and fungal infection of the scalp resulting in cicatricial alopecia. He was diagnosed as nephrotic syndrome 6 months back. He went into remission with steroid therapy, but was inadvertently taking steroids in high doses for 5 months. When the dose of steroid was tapered, patient had relapse of nephrotic syndrome. As per IAP consensus guidelines for steroid sensitive nephrotic syndrome [1], relapse is to be treated with steroids first. As this patient is suffering from serious steroid toxicity already, is it appropriate to use second line drugs straightway?

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RESPONSE TO QUERY

The present patient received inappropriately prolonged therapy with daily prednisolone resulting in severe steroid toxicity. Following stoppage of corticosteroid therapy, he showed a fast relapse, which is a predictor of frequent relapses and thereby further steroid side effects. The management of this patient therefore comprises of induction and maintenance of remission, and prompt therapy for complications of the nephrotic state. Since the disease is expected to resolve by adulthood in most children with steroid sensitive nephrotic syndrome, limiting adverse effects of medications is an important objective of management.

Oral corticosteroids are still the most effective agents for inducing remission in patients with steroid sensitive disease. The response to therapy with prednisolone is predictable and rapid (8-14 days). Other corticosteroid preparations including IV methylprednisolone and deflazacort are not recommended [1,2]. Similarly, there is no experience with the use of cyclophosphamide, levamisole and mycophenolate mofetil for inducing remission in such children. The other class of agents that might be considered for inducing remission is calcineurin inhibitors (cyclosporine, tacrolimus) [2], which reduce proteinuria by 2-4 weeks and induce complete remission by 6-8 weeks. However, the slower response to therapy and associated adverse effects do not justify their use in patients with steroid sensitive nephrotic syndrome. Indications where steroids are avoided for inducing remission, and cyclosporine considered instead, are high blood sugar or steroid psychosis [2].

Once remission is induced, patients with frequent relapses, especially those having steroid toxicity should receive treatment with steroid sparing agents [1-3]. For this purpose, therapy with levamisole, cyclophosphamide, mycophenolate mofetil and calcineurin inhibitors is effective and safe [3]. However, there are few comparative studies on the preferred second-line agent [3], and the choice is determined chiefly by patient and physician preference. Compared to others, treatment with alkylating agents or calcineurin inhibitors offers the best prospect of medium-term steroid free remission [2,3].

The present patient should be treated with prednisolone in the standard dose until remission, and then on alternate days for 4 weeks [1,2]. Subsequently, in order to maintain remission, therapy with oral cyclophosphamide (2-2.5 mg/kg daily) and alternate day prednisolone (20-30 mg/m^2) is recommended. A 12-weeks' course of such treatment is likely to result in sustained remission in a significant proportion of patients. Therapy with calcineurin inhibitors is considered if either steroid therapy is contraindicated (see above) or if frequent relapses recur following cyclophosphamide use. While tacrolimus and cyclosporine show similar efficacy in reducing the frequency of relapses and need for corticosteroids, the latter is preferred in patients with hyperglycemia. Therapy with these agents is, however, initiated after confirming normal renal functions and counseling parents regarding the need for close monitoring.

Additional management includes screening for infectious and other complications. An angiotensin converting enzyme inhibitor is preferred for treating hypertension. The child should consume a balanced diet and be physically active. Parents should be counseled regarding the course of the illness, need for compliance with therapy and adverse effects of medications.

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Congenital Lymphedema : Another Unique and Gender Specific Stigmata of Tuberous Sclerosis?

We report a child of tuberous sclerosis with a rare association of congenital lymphedema and cardiac rhabdomyoma since birth.

A 3-month-old female child, born of non-consanguineous marriage , was detected soon after birth to have nonpitting edema of left lower limb extending from thigh to foot. Neurosonogram and USG abdomen were normal. Echocardiography revealed a 9 x 9 mm rounded pedunculated mass in LV outflow tract, attached to aorto-mitral continuity junction. Physical examination revealed multiple hypopigmented macules in right upper limb and trunk suggestive of ash leaf macules. X-ray chest and ECG was normal for age. Blood investigations were normal. The child's father had a history of seizure disorder and was on antiepileptic drugs. His physical examination revealed hypopigmented to depigmented macules in both upper limbs and trunk, skin colored plaques with irregular border in lumbosacral region and multiple hyperpigmented to erythematous papules and small plaques over face suggestive of ash leaf macules, shagreen patches, and angiofibromas respectively.

Lymphedema is a chronic tissue swelling that is most commonly manifested in a limb. This condition results from impaired lymph drainage in the presence of normal capillary filtration. The three main consequences of lymphatic failure are lymphedema, infection and, very rarely, cancer [1]. Most forms of primary lymphedema are thought to be caused by a congenital abnormality of the lymphatic system and present at or soon after birth. Cardiac rhabdomyomas are intracavitary or intramural tumors that are present in nearly 50 to 70% of infants with tuberous sclerosis (TSC). Most children are asymptomatic. Symptoms are attributed to the presence of intracardiac obstruction, myocardial involvement, and rhythm disturbances [2].

Congenital lymphedema is a rare association with tuberous sclerosis with only few cases reported earlier [3,4]. The previous reported patients were females but unlike our child, they presented with history of multiple seizures while our child had no seizures but instead had a cardiac rhabdomyoma detected incidentally. It is interesting to note that pulmonary lymphangio-myomatosis seen in tuberous sclerosis similarly occurs only in women which is hypothesized to be due to the fact that estrogen regulates TSC gene signalling and, perhaps, also the migration of TSC2-deficient cells [3].

The pathophysiology of congenital lymphedema in tuberous sclerosis is yet unclear. Previous authors have suggested that it could be due to the dysplastic development of lymphatic system in the affected limb as part of TSC gene mutation as this gene regulates cell growth, proliferation and migration. Congenital lymphedema may also be due to the abnormal smooth cell hypertrophy in subcutaneous tissue which externally compresses the superficial lymphatics. An increased awareness of this association may help pediatricians suspect tuberous sclerosis in a female child when congenital lymphedema is the sole external manifestation.

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