Effect of Diethylcarbamazine (DEC) in Relapse cases of Nephrotic Syndrome in Filarial Endemic Region: A case Series

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Author Contribution

This work was carried out in collaboration among all authors. Author JG designed the study and author TV wrote the first draft of the manuscript. Authors DP and AP managed the literature searches. All authors read and approved the final manuscript.

Keywords

Nephrotic syndrome; Diethylcarbamazine DEC; Filariasis; Levamisole; Relapse; steroid sensitive;

Abbreviations

UTI urinary tract infection; DEC diethyl carbamazine citrate; T temperature; AG abdominal girth; URTI upper respiratory tract infection; D.O.A day of admission; CP crystalline penicillin

Abstract

INTRODUCTION- Incidence of nephrotic syndrome and filariasis both is high in China, Japan & India. Studies have shown association of filariasis in NS. In coastal belt of Gujarat, Filariasis occurs as the mosquito responsible is still prevalent. Therefore, filariasis association may be causing persistence of edema in NS relapse cases. After a 7^{th} relapse patient was treated successfully with diethyl carbamazine citrate (DEC), we decided to study, the effect of DEC on weight loss and urine protein, in relapse patients of NS.

MATERIAL METHOD- In relapse patients of NS, DEC was given by oral route in dose of 72 mg/kg/cycle for 7 days. Weight record and urine protein was measured daily. Steroid as Tab prednisolone was administered at 2 mg/k/d.

RESULTS- 1^{st} case was 7^{th} relapse steroid dependant nephrotic syndrome; on prednisolone and levamisole for 3 years. DEC was started on D3 of admission and response seen on D5. Urinary protein became nil on D10, and relapse free since 1 year. In other 4 cases of 1^{st}, 2^{nd}, 2^{nd} and 4^{th} relapse, response of DEC was seen within 2 days. Thus, after starting DEC weight and urine protein reduced within 2 days in 5 relapse cases. Filaria was not detected in blood film of any patient and Elisa test sent in 2 was negative.

CONCLUSION- After starting steroid therapy, no satisfactory response, but after starting DEC, decrease in weight was seen and urine protein became nil within a week. DEC works well in filariasis and has also effects on immune system. Levamisole used as immunomodulator, also acts as an antifilarial agent. DEC may be considered in relapse cases of NS in Filaria endemic regions as it is faster acting, cost-effective and safe.

INTRODUCTION

Nephrotic syndrome is characterized by heavy (nephrotic range) proteinuria as >3.5gm/24hr or a urine protein creatinine ratio >2, hypoalbuminemia (< 2.5 g/dl), hyperlipidaemia (cholesterol >200mg/dl), and edema.[1]

Prednisolone suppresses autoimmunity in nephrotic syndrome & so induces remission early. But long term use of prednisolone can cause steroid toxicity in frequent relapsers, steroid resistant and steroid dependant nephrotic syndrome.[2]

Diethyl carbamazine citrate (DEC) is an anti-parasitic agent used in the treatment of lymphatic filariasis, tropical pulmonary eosinophilia, and loiasis & acts by inhibiting arachidonic acid metabolism. DEC is administered by oral route in the dose of 72mg/kg/cycle spread over 5-15 days (in our study we were giving for 10 m/k/d for 7 days). DEC alters organelle membrane of Mf (microfilariae) and affects muscular activity of Mf. Side effect of DEC due to release of antigens from dying filariae are fever, skin rash, and swollen tender glands in neck, visual disturbance, nausea, dizziness, itching.[3] It is safe in pregnancy.

Levamisole as immunomodulator for nephrotic syndrome is more effective in filarial endemic countries and beneficial effect of levamisole are reported only from south east asia countries.[4] As we see glomerular pathology occurs because of parasitic infections, instead of using levamisole, we can use better specific antifilarial agent, DEC, which has lower side effects.

Method

Here we are discussing effect of DEC in minimal change nephrotic syndrome who had responded to steroids and who presented again with relapse. DEC is not 1st line treatment of nephrotic syndrome here we were using when they came with relapse.

In these 5 cases of minimal change nephrotic syndrome; DEC was administered by oral route in the dose of 72 mg/k/cycle for 7days (Table 1). After starting it, daily weight record and urine protein was measured daily (Figure 3-7). Steroid as Tab prednisolone was administered at 2m/k/d. Investigations are mentioned in Table 2.

Protocol: Each patient was treated as follows in relapse case of nephrotic syndrome:
Prednisolone 2mg/kg/day till remission and then switch over to alternate day therapy. Immunomodulators are continued or added as required. DEC was started in all patients at 72mg/kg/cycle total dose over a period of 7 days.

Course during treatment and Outcome

In the index case A, with 7th Relapse, foci of infection was U.T.I.so treatment for UTI started. Till 4rd day no recovery was seen so considering relapse and no any recovery seen even after starting antibiotics so started DEC on 3rd D.O.A. Edema started to reduce on 5th D.O.A and slowly it disappeared on 8th D.O.A, urinary protein became clear on 9th D.O.A (figure 3).

In 2nd case B, 4th Relapse, foci of infection was chronic tonsillitis so considering bacterial infection we started antibiotics .but no response came so DEC started on 4th D.O.A and after that edema gradually started to reduce on 6th day. (figure 4).

In 3rd case C, 2nd Relapse, foci of infection was UTI and treatment for UTI started. Even after 7 day no any signs of recovery seen so DEC started on 7rd D.O.A and after that edema REDUCED on 9th D.O.A and Urinary Protein became clear on 10th D.O.A (figure 5).

In 4th case D, 2nd Relapse, foci of infection was due to URTI and antibiotic started. Even after 6day no changes in edema and proteinuria seen so DEC started on 6th D.O.A and after that edema started to resolve slowly from 7th D.O.A and Urinary Protein became clear on 9th D.O.A (figure 6).

In 5th case E, admission done and foci of infection was URTI and symptomatic and specific treatment started. But no response till 6th day so DEC started on 6nd D.O.A and after that edema started to reduce on 9th D.O.A & Urinary Protein became clear on 4thD.O.A (figure 7).

No adverse events were detected by using DEC & Filaria was not detected in midnight thick blood film of any patient. Elisa test done in 2 patients was negative.

Table 1: Case Details

History	Examination	Treatment
A.4 Y/F: Eyelid and pedal swelling since 7 day abdomen distension since 2-3 day decrease urine output since 2 days UTI (Ecoli +ve) 7th relapse steroid sensitive	T Normal Eyelids swelling Pedal edema (pitting),transverse umbilicus AG-64cm BP-94/68mmHg	Inj.ciprofloxacin(7day) Tab.levamisole (4day) Tab.prednisolone(2mg/kg/dy)(20mg) (8day) DEC (7day) Tab zinc(12day)
B.2 Y/M: Swelling of eyelid since 3days cough and cold since 2days Tonsilitis 4th relapse steroid dependent	T-Normal AG-64cm BP-96/70mmHg Throat-congested, Tonsil enlarged Eyelids swelling Pedal edema +(pitting)	Inj. Amoxiclav (5dy) Tab.prednisolone (6days) DEC for 7days
C.5.5 Y/M: fever 4day, Eyelid swelling 4 day, Swelling over abdomen 2 day, UTI (urine pus cells) 2nd relapse steroid sensitive	T-Normal AG-64cm BP-96/70mmHg Pedal edema +transverse umbilicus	Inj.ciprofloxacin (10 d) Tab.prednisolone(10 d) Tab.amoxycillin(1day) DEC (7day) Tab zinc(11day)
D.6 Y/F: eyelid swelling-2dy Pedal swelling-2dy Cough-2dy URTI 2nd relapse steroid sensitive	T-Normal AG-60cm BP- 100/70mmHg Throat-congested and Tonsil enlarged Eyelid swelling Pedal edema (pitting)	Inj.amoxiclav(4dy) Tab.prednisolone(4dy) DEC for 7 day
E.6 Y/M: eyelid swelling since 3 day, swelling over abdomen since 3 day tonsillitis 1st relapse steroid sensitive	T-Normal AG-62cm, BP-98/66mmHg Throat-congested PA-visible veins, edema over abdomen, liver+2cm	Inj.CP(5d) Inj.amoxyclav (4day) Tab.prednisolone (9day) DEC (7day)

Doses- Inj.ciprofloxacin- 10mg/kg/d; Tab. Levamisole- 2mg/kg/d, 3d in a week for 6 week; Tab. Prednisolone- 2mg/kg/d; DEC- 72mg/kg/cycle; Tab zinc-10mg/kg/d; Inj.CP-50,000IU/kg/dose

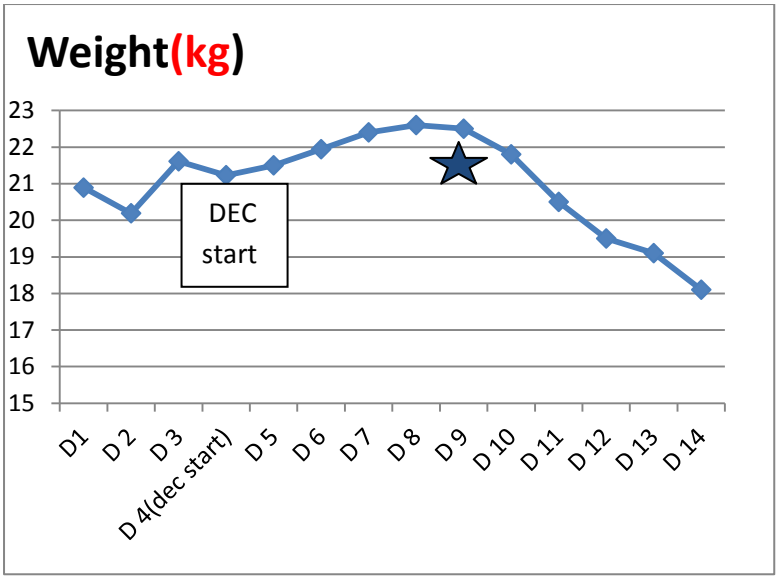
Table 2: Investigations on admission

Investigations	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Total Protein (g/dl)	3.9	4	4.02	3.92	3.2
S. Albumin (g/dl)	1.42	1.5	1.42	1.63	2.1
S. Globulin (g/dl)	2.48	2.5	2.60	2.29	2.8
A/ G ratio	0.57	2.5	0.55	0.71	0.75
S. Cholesterol (mg/dl)	525	385	467	321	320
24hr Urine Protein **(**mg/24hr)	>2000	670	452	395	410
Urine Protein Creatinine ratio (mg/mg)	7.9	9.19	12.85	12.5	8
Weight (kg) Maximum/ on discharge	21.94/18.1	20/18.8	21.3/19.3	20.2/18.2	20.63/18.2

S serum; A/G serum albumin/ globulin ratio

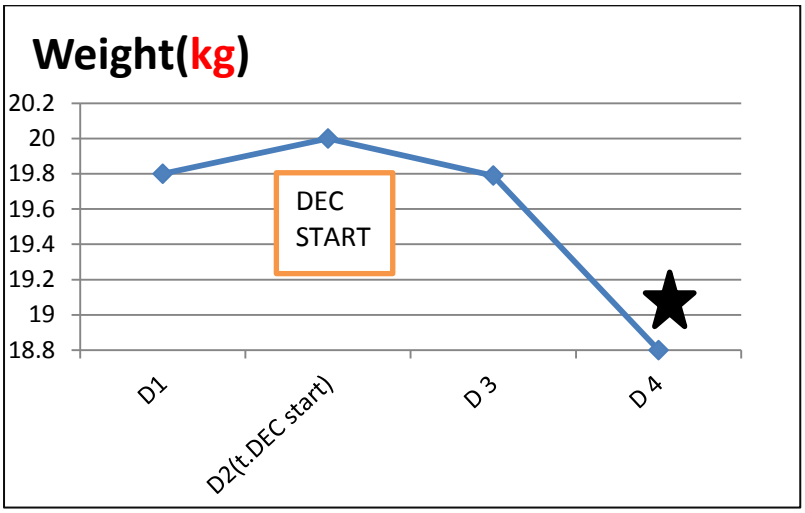
Normal values: T. protein 6-8g/dl; S. Albumin 3.5-5g/dl; S.Globulin-0.5-3g/dl; A/G ratio-0.8-2.0; S. cholesterol <200mg/dl; 24hr urine protein 30-150 mg/24hr; Urine protein creatinine ratio <0.2mg/mg

Figure 3: Case A-4yr female- 7th Relapse



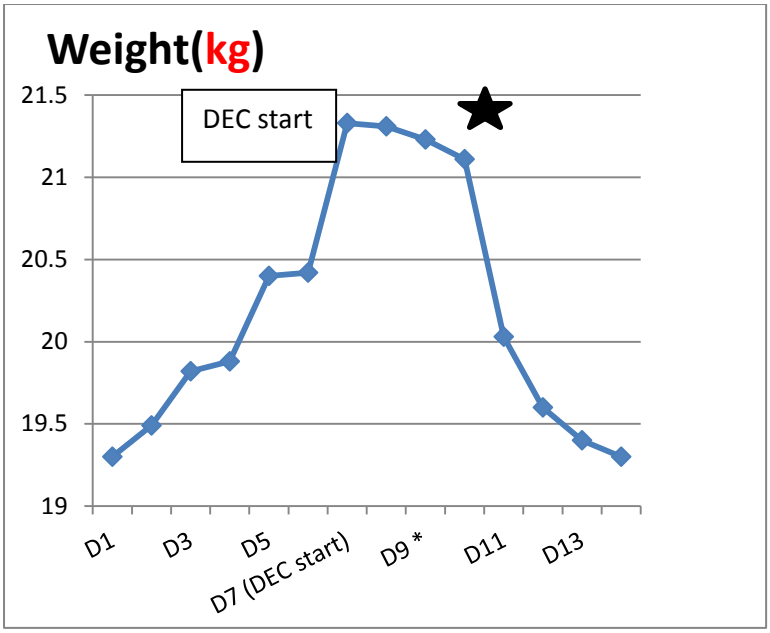
★ ----Shows urine Urinary Protein becomes nil

Figure 4: Case B 2yr male 4th Relapse



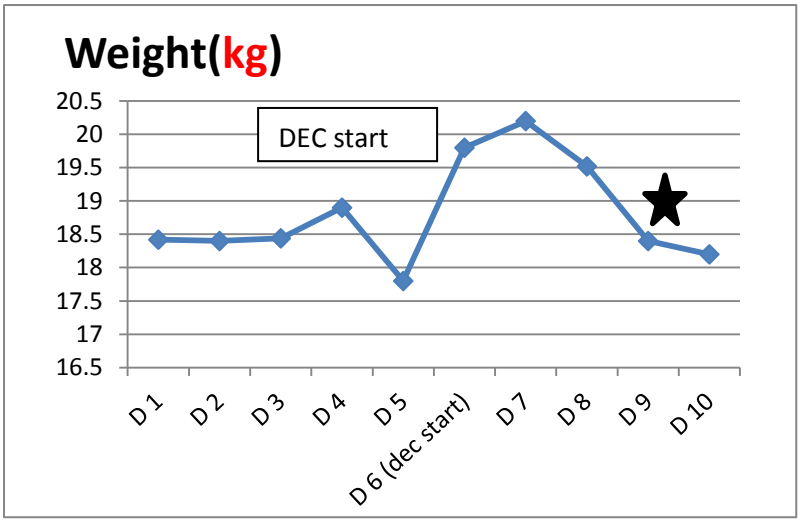
★----Shows urine Urinary Protein becomes nil

Figure 5: Case C. 5.5yr male -2nd relapse



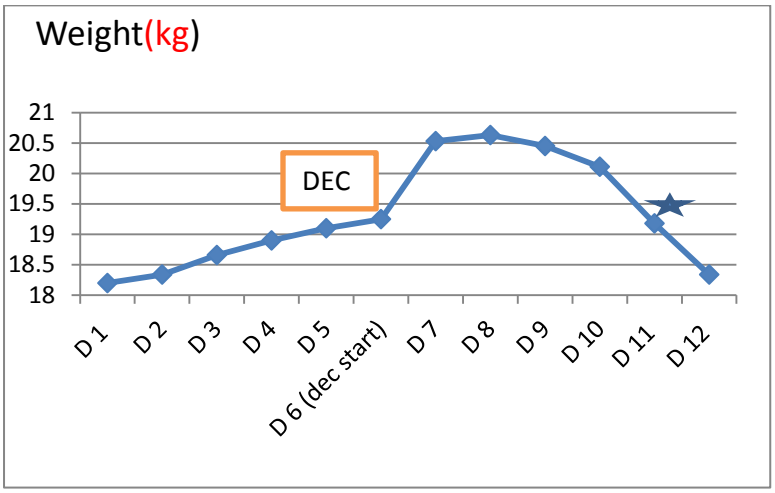
★----Shows urine Urinary Protein becomes nil

Figure 6: Case D -6yr Female – 2nd relapse



★ ----Shows urine Urinary Protein becomes nil

Figure 7: Case E .6yr Male -1st Relapse



★ - Shows urine Urinary Protein becomes nil

Discussion

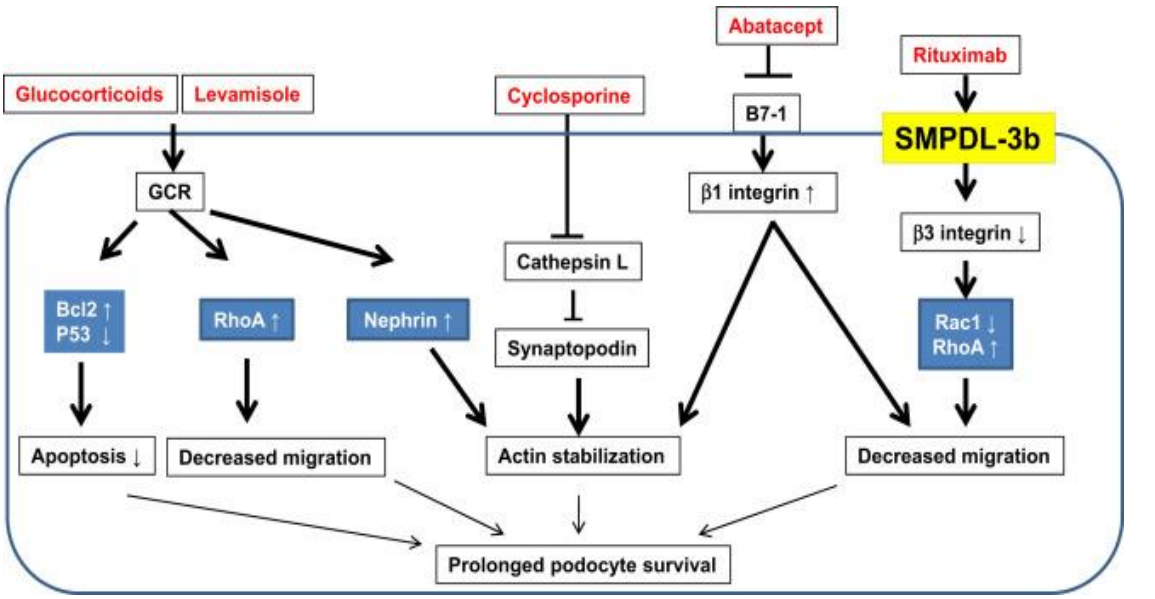
Discussion:

It is a denovo study in nephrotic syndrome patients. Initially reports were done to find out any foci of infection and as per report symptomatic management was done. Still in all these cases edema and heavy range proteinuria, did not disappear so considering connection of nephrotic syndrome with filariasis we started DEC. After starting DEC as effect occur initially weight loss starts slowly and urine heat coagulation becomes clear day by day.

In 1966, new drug levamisole was discovered[5] and due to its immunemodulator property[6], its use had been increased in frequent relapsers, steroid resistant & steroid dependant nephrotic syndrome. But its side effects like leucopenia, rash, seziures limits its use in nephrotic syndrome[7].

As per figure 1 Levamisole attenuates podocyte apoptosis and increase in RhoA (ras homolog family member A) activity and decrease in degradation of synaptopodin protein; and so prolonging podocyte survival[8].

Figure 1 *Mechanism of action of Drugs used in Nephrotic Syndrome (Figure reproduced from 'Nonimmunologic targets of immunosuppressive agents in podocytes' by Yoo TH [8])*

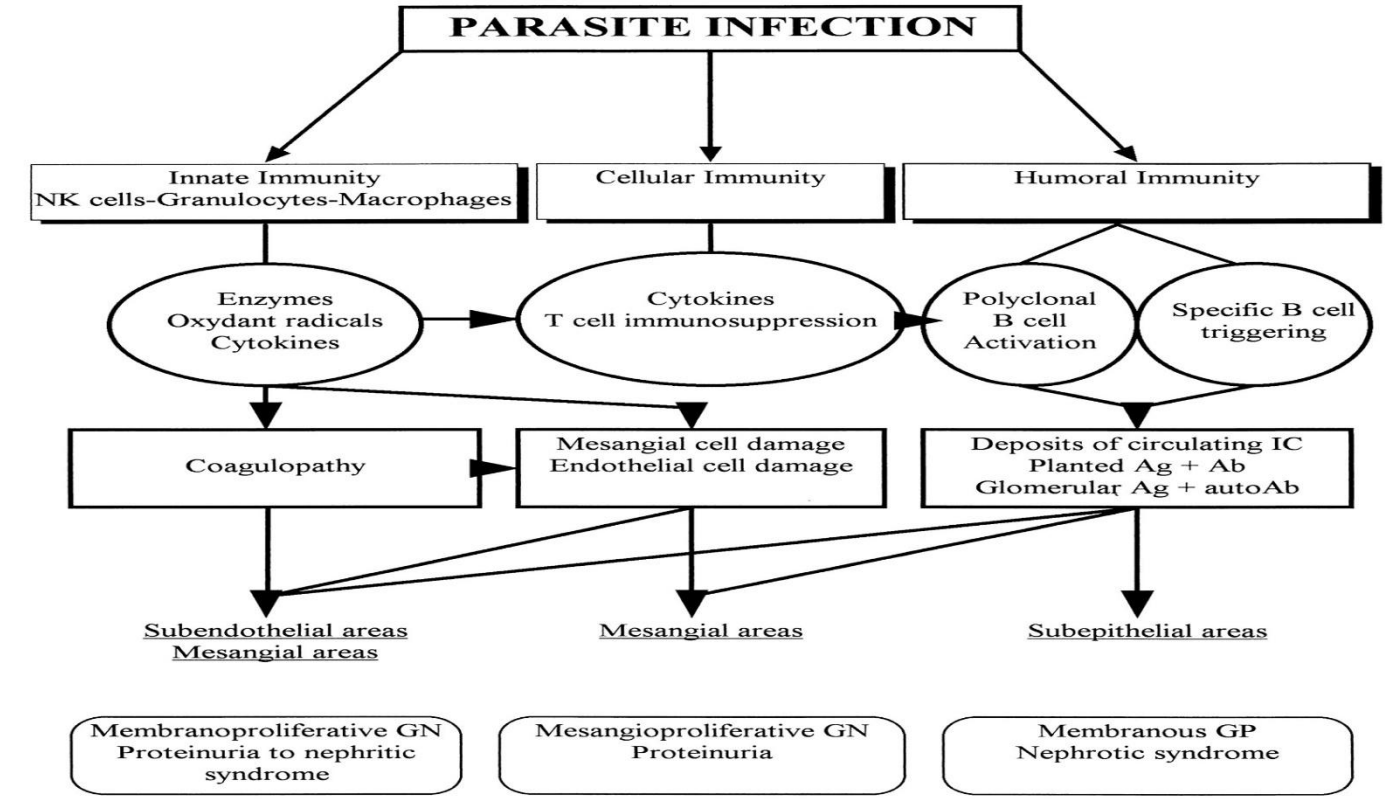


GCR=Glucocorticoid receptor ; Bcl2=B cell lymphoma 2; p53= tumor protein 53; b7-1=membrane protein; RhoA=ras homolog family member A; SMPD-3B=Sphingomyelin phosphodiesterase acid like 3B; Rac1=Rac family small GTPase 1

Incidence of nephrotic syndrome was quite high in China, Japan, India and many Asian countries in 1950s[9]& incidence of lymphatic filariasis was also quite high in those countries.[10] As per figure 2 there is a clear association of filariasis and nephrotic syndrome.[11] In the Coastal belt of Gujarat, filariasis still occurs as the mosquito responsible for it , therefore filariasis association causing persistence of edema in nephrotic syndrome is possible.

After filarial infection of human body the generated toxins affects several compartments of the immune system. And play a role in fighting parasitic infections & in the pathogenesis of associated glomerulopathies. During infection, released inflammatory mediators directly damage the different glomerular cell types & participate in the activation of specific subsets of T and B cells, resulting in different levels of antigen, antibody & immune complexes. Depending on the site of the immune-complex deposition and on the type of primary damaged glomerular cells, different glomerular lesions develop.[12]

Figure 2 *Effect of Parasitic Infection (Figure reproduced from 'The nephrotic syndrome associated with filariasis' study done by Yap HK[11])*



NK cell=Natural killer cell; GN=glomerulonephritis; Ag=antigen; Ab=Antibody; GP-glomerulopathy

DEC works well in filariasis and other parasitic infections and due to serious side effects of levamisole & due to possible association of filariasis with nephrotic syndrome, it can be used in nephrotic syndrome as it is cost effective and safety is better than levamisole.

Conclusion

As per above study, After Starting DEC, weight and urine protein started to reduce within 2 days.
DEC works well in filariasis and has also effects on immune system. Levamisole used as immunomodulator, also acts as an antifilarial agent. DEC may be considered in relapse cases of NS in Filaria endemic regions. It is cost-effective and safe. Further trials with controls and efforts to detect antigen is recommended.

What is already known?

Levamisole is used for steroid dependant nephrotic syndrome. It is also a wormicidal drug acting on filarial worms. Filaria has been linked with minimal change nephrotic syndrome and filarial antigen has been observed in kidney biopsy. Diethylcarbamazine (DEC) is the drug of choice for Filarial infection.

What this case series adds?

The effect of DEC (when added to Prednisolone) in relapse cases of nephrotic syndrome in filarial endemic region appears to reduce edema and proteinuria within 3-4 days of administration. DEC need to be studied in relapse cases in place of Levamisole.

Limitations of study

This is a denovo case series and it is a proof of concept case series. A study with control is recommended which is lacking in this study.

Disclaimer regarding Consent/Ethical Approval:

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

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