Case Report

Congenital Nephrotic Syndrome and Peripheral Veno-occlusive Disease Secondary to Congenital Cytomegalovirus Infection: A Case Report

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Introduction

The term congenital disease refers to the disease that is present at birth or within three months of life. In 85% of the cases, mutation of gene is responsible for the disease. Congenital nephrotic syndrome can be associated with infections that occurred during pregnancy, most important of these are TORCH (Toxoplasmosis, Rubella, Cyto-megalovirus, Herpes simplex) infection[1,2,3,4]. The primary problem in congenital nephrotic syndrome is leakage of protein causing loss of antibodies, hormones, lipids, clotting factors etc and patient manifests symptoms of infection, hypercoagulable state, thrombosis, and hypothyroidism[5,6]. In this case patient had non pitting oedema, peripheral veno-occlusive disease, cyto-megalovirus pneumonia, hypothyroidism all of which led to writing this report as first ever such case diagnosed in Combined Military (CMH) Hospital, Dhaka.

Case History

A six months old baby girl got admitted to Combined Military Hospital Dhaka on 6th September 2014 with the complaints of frequent convulsion at home and gradual swelling of both lower limbs for 3 days. There was no history of fever. The informant mother stated that her daughter developed swelling of right lower limb followed by left lower limb from 27th days of age. Baby was irritable and restless specially on touch to leg due to pain. The patient was initially diagnosed as a case of cellulitis legs. MRI of leg was done which was suggestive of cellulitis. She was treated with broad spectrum antibiotics (Inj Meropenem, Inj Clindamycin) and NSAIDs (Syp Naproxen) with other supportive measures. But after one week baby developed heamaturia associated with nonpitting oedema and puffy face. At that time patient was clinically diagnosed as a case of Drug Induced Nephritis which was managed with fluid restriction, diuretics, ACE inhibitors etc. After recovery from above complaints the patient was discharged. But after about 1 month she developed high fever and cough for which she got admitted to CMH Chittagong and treated with injectable antibiotics and discharged from the hospital. Again after 10-12 days she developed swelling of both the lower limbs and cough associated with frequent afebrile seizure for which she got admitted to same CMH.Then she was referred to CMH Dhaka for evaluation.Patient had severe non pitting oedema in both lower limbs and limbs were tender. Lymphatics channel obstruction, venous channel obstructions and vasculitis were considered as diagnosis. This time the patient was evaluated thoroughly with extensive investigations in CMH Dhaka which included as follows:

1. Complete blood count - anaemia (9.3g/dl), leukocytosis (22.8 x109/L) and thrombocytosis (70x109/L);
2. Serum albumin- 25g/L, serum globulin - 19g/L;
3. Serum cholesterol-248mg/dl, serum triglyceride-264mg/dl;
4. Serum urea creatinine – normal;
5. Serum electrolytes – hypokalaemia(3.4mmol/l);
6. Serum calcium - hypocalcaemia (5.5mg/dl);
7. PT, APTT – prolonged;
8. Urine R/E - RBC and pus cells were plenty;
9. Urine culture - no growth;

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10. TORCH antibody–both IgG & IgM for CMV and HSV were positive;

11. Chest X ray -Suggestive of Pneumonia;

12. Lymphangiogram- normal lymphatic channel;

13. Vascular color doppler upto internal iliac artery–normal;

14. D-Dimer assay – negative;

15. Fibrinogen level - normal (272mg/dl);

16. ANA, Anti DS-DNA, ANCA-C, ANCA-P were normal;

17. Serum C3, C4-normal;

18. Serum TSH - normal (0.65µIU/ml);

19. Serum amylase – normal;

20. HBsAg and anti HCV – negative;

21. C-Reactive Protein – negative;

22. Duplex study of lower limb - diffuse bilateral oedema;

23. Peripheral venography (To exclude oedema from venoocclusion) showed narrowing of peripheral vessels at various levels in both upper and lower limbs with beaded irregular outline of peripheral veins and

24. Biopsy of great saphenous vein – normal.

From above investigation findings, peripheral veno-occlusive disease due to hyperlipidaemia was suspected with second thought of congenital nephritic syndrome. The patient was treated with antihypertensive, anti-coagulant, diuretics, lipid lowering agents, angiotensin-converting enzyme (ACE) inhibitors and acyclovir. (Fenofibrate, Nicotinic acid, Warferin, Asprin, Lasix, Enalapril).

With above management, the patient improved clinically. Her oedema disappeared; urine became yellowish from red, bed side urine albumin reduced, fever and pneumonia (CMV) with superadded bacterial infection subsided. But after two weeks the patient again developed haematuria and puffy face. Her urine output was reduced, liver enzyme increased and nasogastric bleeding started. So, antilipid drugs and anticoagulants were stopped. Next week her lipid profile showed-triglycerides -1385mg/dl, total cholesterol- 476 mg/dl. So the patient was again discussed in clinical meeting (30-10-04) in presence of a visiting Saudi cardiac team. After a long discussion, diagnosis considered were 1. Congenital Nephrotic Syndrome, 2. Familial hyperlipidaemia, 3. Nephritic Nephrotic Syndrome (secondary to hypercholesterolemia or complication of congenital nephrotic syndrome), 4. Vit D deficiency etc.

Treatments with fat free diet, inj Enoxaparin @ 1mg/kg/dose subcutaneously 3 doses, lipid lowering agent Fenofibrate, Nicotinic acid started. Monitoring of liver enzymes was advised as fenofibrate was a hepatotoxic drug. To give benefit of doubt for nephrotic syndrome tab prednisolone-2mg/kg in daily divided doses along with other supportive measures were also started. Medical board also advised for blood protein C and S level, antithrombolysin, PT, APTT, serum amylase, Vit D level and parental screening of lipid profile. All these investigations were found normal. After starting above management, patient's condition improved; oedema subsided, urine output increased, urine colour became normal and albumin disappeared from urine. This kind of improvement was achieved initially also after anticoagulation and antilipid therapy but addition of steroid has given more benefit this time though there is no definite role of steroid in management of congenital nephritic syndrome[6].

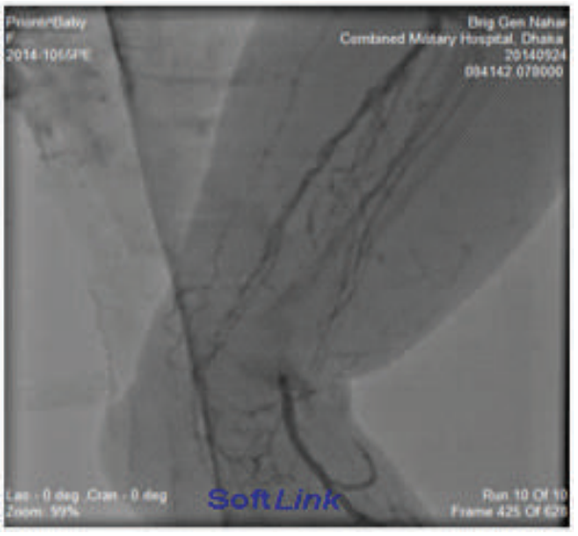
From above investigation and response to treatment, we finally came to following diagnosis.

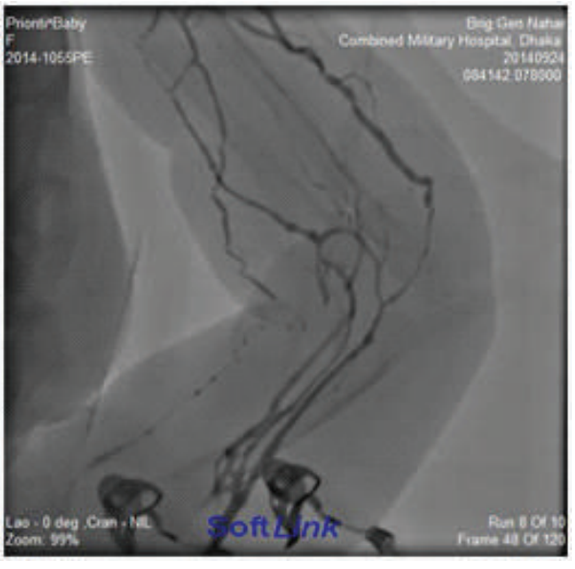
- Secondary Congenital Nephrotic Syndrome due to cytomegalovirus infection (Congenital TORCH infection)
- CMV pneumonia
- Proteinuria leading to hypercoagulable state (loss of clotting factors), veno-occlusion and thrombosis.
- Thrombosis in renal micro vessels leading to nephritic change.
- Proteinuria leading to hypofunction of thyroid gland.

Discussion

In nephrotic syndrome loss of protein in urine leads to hypoproteinemia and oedema[6,7] Nephrotic syndrome in first three month of life is known as congenital nephrotic syndrome[1,2,3,4]. In majority of

cases, congenital nephrotic syndrome results from genetic cause but some cases are due to maternal intra uterine infections, commonly cytomegalovirus infection. But congenital infection with syphilis, toxoplasmosis, human immunodeficiency virus can also present with congenital nephrotic syndrome[3,4,5]. It may also result from infantile SLE or mercury exposure. Congenital nephrotic syndrome of Finnish type is a rare autosomal recessive disease with high infant mortality without aggressive treatment. Location of gene has been mapped recently to chromosome 19q12 - q13 in Finnish families[2]. Congenital nephrotic syndrome presents at birth or within 3 months of life with proteinuria, hypoalbuminaemia and oedema[3,4]. The differential diagnosis include Drash syndrome which consists of triad of Wilm's tumour, male pseudoharmaphroditism and progressive renal failure secondary to diffuse messangial sclerosis[5]. In our patient initial diagnosis of cellulitis of lower limb and then NSAID induced nephropathy diagnosed by the pediatrician confused us for long before coming to real diagnosis. Nonpitting oedema also raised confusion about either lymphatic or venous channel obstruction. Though lymphangiogram was normal, peripheral veno-occlusion in several places of upper and lower limbs again misled us for some time. Primary symptom of oedema in nephritic syndrome is due to loss of protein[7,8,9]. But loss of protein which works as antibodies, clotting factor, hormones leads to recurrent infection, thrombosis, hyperlipidemia etc[1]. In this case, peripheral veno-occlusion is due to thrombosis at various parts of peripheral veins which leads to narrowing of lumen and more oedema. Thrombosis of renal micro vessels leads to nephritic change in this patient. Secondary nephrotic syndrome can resolve with treatment of underlying causes[4,5,6]. . In this case, we used acyclovir for treatment of cytomegalovirus infection. Pneumonia also resolved after this treatment. Later proteinuria disappeared with use of steroid. Hyper-triglyceridemia and thrombosis were treated with Fenofibrate, Enoxaparin and low dose Aspirin. Hypo-albuminemia was treated with albumin infusion. So definitive treatment of CMV infection along with symptomatic management of thrombosis and hypercoagulable state, albumin infusion and steroid, brought relief and apparent cure for our patient. Nutritional management of the patient was also offered by NG tube feeding during her critical stage.





Conclusion

Primary congenital nephrotic syndrome is a severe form of disease. There is no cure and patient may need even removal of kidney to get rid from proteinuria. There is always risk of loss of growth, development, recurrent infection, renal failure and event death. But secondary congenital nephritic syndrome has good outcome if underlying cause can be treated successfully. There is no answer to the question that which treatment protocol is good for the patient. Our case was lucky that after a lot of work up, confusion and delay. Diagnosis was established as a case of congenital nephrotic syndrome secondary to cytomegalovirus infection and she is cured now.

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