Spectrum of Behavioural Abnormalities in Children with Nephrotic Syndrome in South Western Nigeria

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Abstract

Nephrotic syndrome is a chronic childhood disease characterized by relapses and children with this condition tend to have behavioural problems associated with the disease. These behavioural problems are usually not anticipated in most resource limited settings and can be frightening thereby making the children and the caregivers to be distressed.

Seven children with nephrotic syndrome who developed various behavioural abnormalities while on admission were discussed. There were four girls and three boys with age range seven to fourteen years. The abnormal behaviours noted were visual and auditory hallucinations, inappropriate speech and behaviour, attempted suicide, attention seeking behaviour and social withdrawal. These behavioural abnormalities were related to prednisolone therapy in five of the children. Diagnosis made were psychosis and delirium while treatment given included counselling, Risperidone, Haloperidol, Diazepam and reduction or withdrawal of Prednisolone.

Abnormal behaviour was not anticipated in these children so the caregivers were taken unaware. This can be worse in infants or in mild cases. Most of the behavioural abnormalities were also associated with the use of prednisolone. There is an urgent need to design guidelines for the management of behavioural abnormalities in nephrotic syndrome especially steroid therapy in resource limited settings. Harmonisation of the skills of paediatric nephrologist and child psychiatrist is also important to obtain the best outcome.

INTRODUCTION

Children with chronic health conditions have a higher tendency to develop behavioural and psychiatric problems [1,2]. They are three times more likely to have behavioural problems compared with other children [3]. The extent of these behavioural abnormalities depends on the duration of the disease and its treatment [4]. Nephrotic syndrome is a common chronic childhood glomerulopathy characterized by massive proteinuria, hypoproteinemia, hyperlipidaemia and oedema. Children with nephrotic syndrome have relapses which makes the diseases chronic coupled with the various procedures that they undergo in the management process. This is what predisposes them to behavioural problems. We present seven children with nephrotic syndrome who developed behavioural abnormalities in the course of their management.

CASE PRESENTATION

AM1 was a 14 year old boy who presented with a 3 months history of body swelling. This was occurring for the first time with no reduction in urine output and no fever. He was on herbal medication with no improvement so he presented at the hospital.

Examination at presentation showed anasarca with mild palour. The cardiovascular system findings were normal. There was abdominal wall oedema and liver was palpable 5cm in the abdomen, non tender and normal bowel sounds. Chest and central nervous system examinations were normal. Urinalysis showed blood 3+, protein- 2+, PH – 6, SG- 1.025 Other parameters were normal

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Urine microscopy, culture and sensitivity revealed wbc – 2-3/ hpf, rbc – 12 – 14/hpf. Culture yielded no growth. The 24 hour urinary protein and plasma creatinine were 2.9g/24 hours and 0.7 mg/dl respectively.
Abdominal ultrasound scan showed ascites with no abnormality of the organs. Initial E/U/Cr - mild acidosis and azotaemia. FBC, PT/PTTK - Normal. Diagnosis was nephrotic syndrome. He had renal biopsy. While awaiting the result, he was commenced on oral Prednisolone at 60mg/m²/day and oral diuretics. He developed hypertension 20 days into the therapy and was commenced on Nifedipine and Elanapril. There was no remission so Prednisolone was reduced to 40mg/m²/day on alternate days after the initial 4 weeks course.

He became withdrawn on the 23rd day of the alternate day prednisolone and the child Psychiatrist made an assessment of mild depression for which he was counselled. However, he developed disruptive behaviour and some non-goal directed activities like cutting tissue paper into bits and spitting around. He was also confused and had insomnia. There was no family history of psychiatric illness. An assessment of delirium secondary to steroid use was made. The Prednisolone was tapered off and he had a stat dose of Diazepam and Haloperidol. He was also commenced on Risperidone. The symptoms gradually resolved over 48 hours. Renal biopsy histology showed focal segmental glomerulosclerosis.

OS1 was a 12 years old boy who presented with facial swelling of 5 weeks and generalized body swelling of 3 weeks. The facial swelling was worse in the mornings, regressing as the day progress and there was no previous history. The urine was described as 'foaming' and the volume was reduced. There was a history of ingestion of herbal preparations prior to onset of symptoms.

Examination revealed that he was mildly pale with anasarca. He was not dyspnoeic with respiratory rate of 28/min. He had reduced air entry in middle and lower lung zones. Peripheral pulses were of moderate volume, heart rate was 120/min, blood pressure was 130/100mmHg and normal heart sounds. Ascites was demonstrable by fluid thrill and central nervous system was normal.

Investigations revealed -
-Total serum protein - 3.3g/dl, Albumin - 1.4g/dl
-Urinalysis - protein 3+, PH 5.0, SG -1.010; 24 hour urinary protein – 82mg/dl – 1.2g/day
-Urinary creatinine – 30mg/dl, Plasma creatinine – 1.1mg/dl
-Creatinine clearance – 220mls00./min
-Fasting lipid- Cholesterol - 447mg/dl (normal - 150-250), Triglyceride - 307 mg/dl (normal 50 – 200), HDL - 12 mg/dl (normal 45-80), LDL - 374 mg/dl (normal 70-120)
-E/U/Cr Na+ 130mmol/L, K+ - 4.4 mmol/L, Cl- - 103 mmol/L, HCO3- 20; Urea- 16mg/dl,Cr- 0.4mg/dl
-24 hour urinary protein- 400mg/dl= 6.6g/24 hours; 24 hours protein/ creatinine ratio-25.1; Creatinine clearance – 59ml/min
-Total serum protein- 6.2g/dl; serum albumin- 1.3g/dl
-Urine microscopy, culture and sensitivy - sterile
-Chest x-ray- left lamellar effusion

A diagnosis of nephrotic syndrome was made. She was commenced on oral Hydrochlorothiazide and Spironolactone. Fresh frozen plasma was given at 10ml/ kg four times with gradual reduction of the oedema. She was commenced on oral Prednisolone at 60mg/m²/day. He completed 4 weeks of this and was to have 2 more weeks as he was yet to go into remission.

He was noticed to have abnormal behaviour in the 5th week of Prednisolone use as he washed his hands on the floor and defaecated on the bed. He also had visual hallucination as he complained of seeing snakes on the ward. There was no family history of psychiatric illness. The Prednisolone was reduced to 40mg/m²/day and these symptoms subsided within 48 hours. He was discharged in the next few days and is being followed up in the clinic.

OS2 is a seven year old girl who presented with swelling of the face, abdomen and leg of four days and the swellings regress with ambulation. There were no other associated symptoms. Examination revealed anasarca with the abdomen distended and both liver and spleen were palpable 4 cm below the costal margins. All the other systems were normal. Investigations showed urinalysis-protein 2+

Electrolytes (mmol/L)- Na-132, K- 4.4, Cl- 103, HCO3_2 - 20; Urea- 16mg/dl,Cr- 0.4mg/dl
-24 hour urinary protein- 400mg/dl= 6.6g/24 hours; 24 hours protein/ creatinine ratio-25.1; Creatinine clearance – 59ml/min

OE was a seven year old boy who presented with progressive body swelling of month duration. This swelling regresses as the day progressed. There was a history of passage of dark coloured urine and reduction in urine volume. There were previous episodes of body swelling at 12 and 18 months of age. Examination revealed that he was mildly pale with anasarca, respiratory and pulse rate were 52/min and 104/min respectively. The blood pressure was 100/70mm Hg. The abdomen was grossly distended with the scrotum and penile shaft oedematous. The other systems were normal.

At investigation, urinalysis showed protein- 4+, blood-1+
-24 hour urinary protein- 160mg- 2.3g/24 hours;
-24 hours creatinine clearance-28ml/min- 66.4ml/min/1.73m²
-Electrolytes (mmol/L)- Na-127, K-3.5, Cl- 102, HCO3_2 - 20; urea- 28mg/dl; creatinine-0.8mg/dl
AJ was a 12 year old girl with a diagnosis of steroid responsive nephrotic syndrome (average relapse in a year is 3 episodes) with each episode usually managed with 4 – 8 weeks of oral prednisolone. She presented with facial and leg swelling of 2 weeks. Examination showed both periorbital and pedal oedema with a blood pressure of 100/70mmHg. Urinalysis revealed protein 4+ and blood 2+ but urine microscopy was normal. Total serum protein was 5.3g/dl while albumin was 2.0g/dl.

Electrolytes (mmol/L)- Na-138, K-3.8, Cl- 104, HCO3- 21; urea-10mg/dl, creatinine-0.6mg/dl fasting lipids (mg/dl)- serum cholesterol-585, triglycerides- 249, HDL- 40, LDL- 495.

A diagnosis of nephrotic syndrome in relapse was made and she was commenced on oral prednisolone. She went into remission on the 7th day and was switched to alternate day prednisolone. She developed psychiatric symptoms after the discontinuation of prednisolone and there was attempted suicide. She also developed attention seeking behaviour. She was managed with Risperidone and counselling with good response.

AB was an eight year old girl who presented with generalized body swelling of 4 months and difficulty in breathing of 3 days. The body swelling regressed with ambulation. There was no reduction in urine output and no previous similar history. The difficulty in breathing progressively worsened before presentation but there was no cyanosis. Examination showed a chronically ill child with fluffy hair, mildly pale, with generalized oedema. She was dyspnoeic, respiratory rate was 22/minute, percussion notes were resonant and breath sounds were vesicular. There were normal volume pulses with rate of 120/minute and blood pressure of 130/80mmHg. The heart sounds were normal. Her abdomen was distended with the organs difficult to palpate and ascites demonstrable by fluid thrill. The child was conscious but lethargic. The initial diagnosis was nephrotic syndrome with hypertension to rule out chronic glomerulonephritis.

Urinalysis showed protein of 3+ and blood 1+. Total protein-4g/dl, albumin- 0.8g/dl. Electrolytes (mmol/L)- Na-138, K-3.1, Cl-109, HCO3- 18; urea-11mg/dl, creatinine-0.5mg/dl

Serum cholesterol- 260mg/dl, Chest x-ray was normal.

She was commenced on IV frusemide, oral hydrochlorothiazide, spironolactone and nifedipine with intranasal oxygen. Hypertension resolved after seven days. The child however developed both auditory and visual hallucination on the 9th day on admission; assessment of child psychiatrist showed she had delirium secondary to the general medical condition. She was commenced on Risperidone and the hallucinations stopped. The drug was tapered off after 8 days. She then commenced oral prednisolone but did not go into remission after 30 days of the drug. She is presently being followed up in the clinic.

AM2 was a 9 year old girl diagnosed with nephrotic syndrome at 2 ½ years of age and has had several relapses. The parents refused definitive treatment. She presented with history suggestive of degenerating renal function (persistent anaemia unresponsive to haematinics, occasional hypertension, weakness and vomiting). Examination revealed that she was very ill, cachexic, had fluffy hair and was mildly pale with generalised muscle wasting. The respiratory rate was 18/min, pulse rate- 90/min and blood pressure- 100/60mmHg. She was conscious but weak. The initial diagnosis was nephrotic syndrome with likely chronic kidney disease and electrolyte derangement.

From the investigations, urinalysis showed protein 3+ and blood 2+; urine microscopy, culture and sensitivity revealed hyaline and waxy casts.

Electrolytes(mmol/L)- Na-118, K-1.9, Cl-75, HCO3-17; urea-110mg/dl, Cr-1.8mg/dl, Ca-7.1mg/dl, PO4- 3.8mg/dl

Fasting Lipid profile- cholesterol- 274mg/dl, triglycerides-372mg/dl Total serum protein-6.6g/dl, albumin- 2.2 g/dl

Renal biopsy histology- focal segmental glomerulonephrosis with interstitial fibrosis progressing to end stage kidney disease.

Other investigations were normal.

She was admitted and had electrolyte derangement corrected. Inappropriate speech and behaviour was noticed on the third day on admission despite the fact that she had a normal random blood sugar and electrolytes. She was reviewed by child psychiatrist who made a diagnosis of acute psychosis secondary to the nephrotic syndrome and she was placed on haloperidol with a good response. She eventually had a trial of steroids but did not achieve remission. She was later lost to follow up.

**DISCUSSION**

Behavioural abnormalities in nephrotic syndrome may be as a result of psychological reaction to the chronic illness [4-6] as seen in AB and AM2. Nephrotic syndrome, being a prolonged disease condition will require prolonged intake of medication, frequent hospital visits with regular blood sample collection for investigations and sometimes surgical procedures like renal biopsy which is used for confirmatory diagnosis. All these can constitute psychological stress to these children. The children may also feel irritable by perceiving their parent’s continuous concern about their health. The physical changes from the disease like facial puffiness, pedal oedema and cushingoid transformation from steroid use can lead to being jeered at by their peers especially in adolescents as seen in AJ and lead to challenging psychosocial problems, constituting an indirect mechanism for abnormal behaviour [5]. The disease can also lead to alteration in normal daily activities which may not allow the child to be able to engage in play activities and also result in school absenteeism. This can result in poor academic performance which can also be the cause of psychological
problems resulting in behavioural abnormalities [7]. Prolonged use of high dose steroid in the treatment of nephrotic syndrome exposes children to the various side effects of prolonged steroid use including steroid psychosis (this is seen in AM1, OS1, OS2 and OE). The cause of the behavioural changes arising from steroid use is not known, but the hippocampus, the septum and amygdala have been implicated [4]. These areas of the brain have dense receptors for corticosteroids [5,8] and are involved in mood, behaviour and memory functions of the brain. The hypoalbuminemia seen in nephrotic syndrome causes a high level of unbound prednisolone which will bind to the receptors in the earlier mentioned areas of the brain [4,9]. Corticosteroids are also known to alter the brain excitability and affect the CNS levels of some neuropeptides and neurotransmitters leading to behavioural problems [9]. The onset of symptoms varies from few days to 4 weeks of commencing high dose steroids [10,11] and sometimes symptoms appear when the tapering of steroids commences due to their psychological dependency from their euphoric effects as found in AM1 and AI. The mainstay of treatment for steroid induced psychosis is to reduce the dose of the steroid or discontinue it [8,10,12]. Psychoactive drugs have been used when discontinuation of steroids alone is not enough but with variable outcomes [13]. Risperidone have been used successfully and it has the advantage of rapidly acting even at low dose with absence of significant discontinuation syndrome [14]. Electroconvulsive therapy have also been employed in severe cases of psychosis with good results [14,15].

Behavioural abnormalities that is associated with nephrotic syndrome varies and can range across pathology like mood liability, anxiety symptoms, cognitive impairment, behavioural disturbances and psychotic features either alone or in combination [16]. Mild to moderate symptoms include anxiety, agitation, insomnia, irritability and restlessness, while severe symptoms include depression and psychosis [12]. The symptoms vary with affective symptoms (emotional liability, grandiosity, pressured speech, suicidal ideation, irritability) being most common and psychiatric symptoms (persecutory, delusions, hallucinations) being less frequent, though it has been observed that compulsive behaviour are predominant in children [11]. There can also be periods of altered consciousness and disorientation. These symptoms can actually fluctuate dramatically during the course of the illness [10]. Boys tend to show more hyperactive and aggressive behaviours than girls and the risk of developing behavioural abnormalities is slightly higher in girls and younger children [9]. The symptom duration also varies as delirious ones recover within few days of intervention whereas psychosis usually takes more than one week to recover [10]. Children in most studies have no previous or family history of psychiatric disorders [10,17,18].

The input of child Psychologists in the management of behavioural abnormalities associated with nephrotic syndrome is very valuable as they have a vital task of assessing the clinical significance of the children’s behaviour [15]. Good nursing care by mental health trained staff also have important role to play [6]. Unfortunately, paediatric liason services which handle the psychological health needs of children with chronic diseases barely exist in sub Saharan Africa [19]. This implies that even in facilities where these expertise are found, their inputs are not being harmonized with the skills of the paediatricians looking after children with nephrotic syndrome and other chronic diseases. This does not augur well for the care of these children as psychological care is better started at the earliest stage of these diseases, there is no advantage in waiting until they develop behavioural problems [20].

The nature of these behavioural abnormalities makes them very important as they can be frightening and distressing to the caregivers and the child. Anticipatory guidance can be given to parents about potential behavioural problems and this can allow them to be better prepared for these problems both at home and in school. Health care staff should engage in proactive questioning about mood and behavioural symptoms as stigma and difficulty in recognition, especially in younger children may limit spontaneous reporting by parents. Additional support should be given during periods that children have behavioural abnormalities which could be of great concern to caregivers.

The proper use of anticipation with timely and effective intervention will greatly reduce the stress of behavioural abnormalities experienced by children with nephrotic syndrome.

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REFERENCES


