Nigerian Journal of Paediatrics 2007; 34(1&2): 31-35

Prevalence of Nocturnal Enuresis in Children with Homozygous Sickle Cell Disease in Zaria

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Summary

Ogunrinde GO, Zubair RO, Mado SM, Musa S, Umar LW. Prevalence of Nocturnal Enuresis in Children with Homozygous Sickle Cell Disease in Zaria. *Nigerian Journal of Paediatrics* 2007; 34: 31.

Background: Nocturnal enuresis (NE) is believed to be commoner in children with homozygous sickle cell disease (SCD-SS) than in those with normal haemoglobin. The reasons for this have not been established and its prevalence and pattern have not been adequately described in the tropics.

Objective: To determine the prevalence and describe the pattern of nocturnal enuresis in children with SCD-SS in the Guinea Savannah region of Nigeria.

Method: A cross-sectional case-controlled study was carried out on randomly selected steady-state children with SCD-SS attending the Haematology Clinic of the Department of Paediatrics at Ahmadu Bello University Teaching Hospital, Zaria. A structured questionnaire was used to collect historical and clinical data from the patients. Age-dependent definition of NE was used in analyzing data.

Results: One hundred and fifty (47.1 percent) of the 360 children with SCD-SS studied had NE. The rate was significantly higher than that obtained in control children. Whereas significantly more male than female control children had NE, the difference did not reach statistical significance in those with SCD-SS. Many home caregivers used potentially harmful methods in attempts to control NE. Socioeconomic factors and family history did not play significant role in the prevalence of NE.

Conclusion: Nocturnal enuresis is commoner in children with SCD-SS than in otherwise normal children, even in the Guinea Savannah region of Nigeria. It is suggested that NE in SCD-SS may not be innocuous.

Introduction

STRUCTURAL damage to the kidneys of the individuals with homozygous sickle cell disease (SCD-SS) has been documented.[1] Probably as a result, children with SCD-SS develop hyposthenuria which usually manifest early as enuresis.[2] Nocturnal enuresis has been reported as being more common in children with SCD-SS than in otherwise normal children. However, most of the studies have been carried out in developed countries.[3-5] We, therefore, undertook a cross-sectional study to determine the prevalence and pattern of nocturnal enuresis in children with SCD-SS living in a tropical region located in the Guinea Savannah belt of this country.

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Patients and Methods

The study was carried out in the Paediatric Haematology Clinic of Ahmadu Bello University Teaching Hospital, Zaria. Based on the study reported by Akinyanju *et al*,[3] 34.9 percent was estimated to be the prevalence (p) of enuresis in children with SCD-SS. From this estimate, a minimum sample size of SCD-SS patients to be studied was calculated to be 350 using the following formula:[6]

$$n = \frac{Z^2_{\alpha/2} \times p \times (1-p)}{d^2}$$

where $Z_{\alpha/2}$ is the standard normal variable, and at 95% confidence interval is equal to 1.96, p is the estimated prevalence, and d is the degree of precision, and is equal to five percent for the purpose of this study. Out of the approximately 30 attendees at the weekly clinic, 10-12 children with confirmed haemoglobin phenotype

SS or SS+F were randomly selected. Informed consent was obtained from the accompanying home caregiver. A structured questionnaire was administered by the researchers seeking for such information as the age of the child, socioeconomic and educational status of the parents, presence of nocturnal bed-wetting, frequency of bed-wetting in the three months before recruitment into the study, family history of nocturnal bed-wetting, location of toilet facilities in respect of place of abode, history suggestive of perinatal asphyxia and the age at which the child started walking. Any patient aged less than 60 months or who had any crisis in the three months prior to the study was excluded from the study.

Age-matched control children were randomly selected from the Paediatric Outpatient Clinic of the same hospital the day after the Haematology Clinic. After selecting patients in the age range of the subject with sickle cell disease (± three months), random selection by ballot paper was then made. Ten control children with minor ailments were selected on a weekly basis. The controls were examined and were excluded from the study if they had clinical features suggestive of renal, cardiac, neurologic or hepatic disorder. Only control children with confirmed haemoglobin genotype AA were included. The haemoglobin genotype was either in the control's medical record before or requested for, during the study. For the purpose of this study, nocturnal enuresis was defined as three or more episodes of bedwetting monthly in a child aged 5-6 years and at least, once monthly in an older child.[7] In either case, the bed-wetting must have been present for at least three months for the child to be recruited for the study. The child was considered to have primary enuresis if he had not stopped bed-wetting and secondary enuresis if he had stopped bed-wetting for at least six consecutive months anytime in his life.[7]

Chi-square test was used to analyse categorical data while Student's t test was used for continuous variables such as means. A p-value of less than 0.05 was taken as significant.

Results

A total of 360 children with SCD-SS and 237 with haemoglobin AA were studied. The baseline characteristics of the two groups are shown in Table I. The characteristics of the two groups are not significantly different except that subjects mostly came from large-sized families, defined for the purpose of this study as families with more than four children ($p = 0.001$).

One hundred and fifty (41.7 percent) of the 360 SCD-SS patients had nocturnal enuresis and this rate was significantly higher than the 17.7 percent (42 of 237 children) obtained in the control group ($p < 0.00001$). Majority of children with SCD-SS (75.5 percent) and majority of controls (64.3 percent) had primary nocturnal enuresis; the difference in rates was not statistically significant. Figure 1 shows the pattern of age-related decline in prevalence of nocturnal enuresis in the two groups of children. After the age of 84 months the prevalence in control children dropped rapidly to zero while it virtually plateaud in the SCD-SS individuals and dropped slowly after the age of 144 months, with the oldest child with nocturnal enuresis being 202 months (16 years and 10 months).

Among the control children, significantly more males (27 of 106; 25.5 percent) than females (15 of 131; 11.5 percent) were enuretic ($p = 0.008$). Even though more male SCD-SS children (86 of 184; 46.7 percent) than female (64 of 176; 36.4 percent) were enuretic, the difference did not reach statistical significance ($p = 0.06$). Sixty-four (36.4 percent) of 176 females with SCD-SS and 15 (11.5 percent) of 131 female controls had nocturnal enuresis, with the rate in the female subjects being significantly higher ($p = 0.000003$). The difference between male SCD-SS subjects (86 of 184; 46.7 percent) and male controls (27 of 106; 25.5 percent) was also significant ($p = 0.0006$). Significantly less SCD-SS patients in this study had history suggestive of perinatal asphyxia ($p=0.0002$) but, paradoxically, started walking at a significantly older age than the control children ($p < 0.00001$).

In 63 (42.0 percent) of the 150 enuretic SCD-SS children, the home caregivers perceived the nocturnal enuresis to be abnormal, compared with nine (21.4 percent) caregivers of enuretic control children ($p = 0.02$).

Table II shows the various reasons adduced by home caregivers for the nocturnal enuresis in their wards with SCD-SS. Drinking too much fluid, sleeping too deeply and climatic effects were the most common reasons. In only 6.4 percent of instances was the enuresis suggested as being a consequence of the sickle cell anaemia. Table III shows the various remedies applied by the home caregivers in attempts to stop nocturnal bed-wetting in this study. Most of the caregivers used a combination of methods to get their wards to stop bed-wetting. The commonest methods employed are waking up the child to urinate many times in the night, getting the child to urinate before retiring for the night. A lot of caregivers also scolded or/and spanked the children for wetting their beds at night.

There was no significant difference in the frequency of positive family history of nocturnal enuresis in enuretic children of either group. In both groups, there were negative histories in the majority of children: 77.6 percent in SCD-SS and 78.6 percent in

the 384 children) were receiving highly active antiretroviral therapy; 10 of the remaining 50 died and the remaining 40 were lost to follow up before commencement of antiretroviral drugs.

With regard to the outcome, 278 (72.4 percent) of the children were still alive and being followed up, 67 (17.4 percent) were lost to follow up (LTFU), while 27 (7.0 percent) have died. Twelve (3.1 percent) seroconverted and have been discharged from the clinic. The greatest percentage of deaths (74.1 percent) occurred in those who were aged less than 18 months, three (11.1 percent) were in the 18-59 months age group, while four (14.8 percent) were aged 60 months and above. The age specific mortality was highest among the less than 18 months old although there were no significant differences among the different age groups (Fishers exact test p=0.35). Fifty (74.6 percent) of the 67 who were LTFU, were aged under 18 months, 10 (14.9 percent) in the 18- 59 months age bracket, and seven (10.4 percent) were aged 60 months and above. This difference was not statistically significant among the different age groups (x2 = 0.11, df 1, p= 0.744).

Table IV

Symptoms and Signs in the 336 Symptomatic Children#

Symptoms	*No=336 (%)*	*Signs*	*No=336 (%)*
Fever	253 (75.3)	Lymphadenopathy	148 (44.0)
Cough	218 (64.9)	Pallor	132 (39.3)
Weight loss	138 (41.1)	Hepatomegaly	128 (38.1)
Diarrhoea	137 (40.8)	Oral thrush	80 (23.8)
Rashes	118 (35.1)	Parotid swelling	23 (6.8)
DDMS	31 (9.2)	Splenomegaly	16 (5)
CSOM	29 (8.6)	Hypotonia	15 (4.5)
Seizures	20 (6)	Hypertonia	10 (3)
RDMS	14 (4.2)	Deep seated ulcers	4 (1.2)

Delayed developmental milestones
CSOM – Chronic suppurative otitis media
RDMS – Regression in developmental milestones
Some patients had multiple symptoms/signs

Table V

**Co-Morbidity/Contributors to Case Fatality*

Cause	*Morbidity n 384 (%)*	*Mortality n 27 (%)*
Tuberculosis	91 (23.7)	8 (29.6)
Pneumonia	59 (15.4)	12 (44.4)
Encephalopathy	45 (11.7)	8 (29.6)
Malnutrition	42 (10.9)	9 (33.3)
HIVAN	8 (2.1)	4 (14.8)
Septicaemia	5 (1.3)	5 (18.5)
PCP	20 (5.2)	-
Hepatitis B	4 (1)	-
Hepatitis C	4 (1)	-

* Some children had more than one co-morbidity
HIVAN = HIV-associated nephropathy
PCP = Pneumocystis carinii pneumonia

Discussion

Paediatric HIV/AIDS is a significant cause of morbidity and mortality in UPTH. In the present study, there was no gender difference, a finding that is similar to observations in other parts of Nigeria, such as Nnewi[5] and Jos [10] but is at variance with results of studies carried out in Ife[18] where there was a female preponderance and findings in Zaria[8] and India [19] where male preponderance was reported. The predominant mode of transmission in this study was vertical. This is in agreement with other studies in Nigeria[5,8-10] and India.[19,20] It is an established fact that vertical transmission is the major mode of transmission of HIV in children. This means that in order to reduce HIV infection in children, emphasis should be on effective and readily available prevention of mother to child transmission of HIV (PMTCT) programme. Women represent the fastest growing

Table II

Reasons proffered by Home Caregivers for Enuresis in their Wards

Reason for Enuresis	*Number (%)*
Too much fluids	54 (19.1)
Too much sleep	51 (18.0)
Delayed development	34 (12.0)
Weather	33 (11.7)
Ill-health apart from SCA	24 (8.5)
SCA	18 (6.4)
Laziness	18 (6.4)
Familial	15 (5.3)
Don't know	12 (4.2)
Others	24 (8.5)

SCA = Sickle cell anaemia

Tables III

Remedies used to address Enuresis in Sickle cell Anaemia

Remedy	*Number (%)*
Intermittent waking during the night	132 (30.3)
Urination before retiring	108 (24.8)
Scolding	81 (18.6)
Spanking	51 (11.7)
Withholding fluids	39 (9.0)
Self-medication	9 (2.1)
Early-morning waking	6 (1.4)
Report to health worker	3 (0.7)
Positive reinforcement	3 (0.7)
Report to a neighbour	3 (0.7)

controls. One hundred and twenty (80.0 percent) of enuretic SCD-SS children lived in self-contained houses where the toilet facilities were located within, and 30 (20.0 percent) where they were located outside the four walls of the house. A similar pattern was observed in the control group with 71.4 percent living in self-contained apartments.

Discussion

This study has demonstrated that in the Guinea Savanna region of Nigeria, children with sickle cell anaemia have a significantly higher rate of nocturnal enuresis compared to children with normal haemoglobin and confirms the findings of Akinyanju *et al* in the southwestern part of the country,[3] even though the definition of enuresis used in the present study differed from the one used by these earlier workers. The result is also in keeping with the higher prevalence of nocturnal enuresis observed in SCD-SS children in other parts of the world.[4,5] It has been shown in this study that just like in the normal population,[8] children with SCD-SS have primary nocturnal enuresis more commonly than do those with the secondary variety. The study did not however, set out to investigate the causes of these cases of secondary nocturnal enuresis and as such no differentiation was made in the analysis of data. As a result of the varying definitions of enuresis used by different workers, direct comparisons between our study and others would be difficult. The variation in diagnosis is due to lack of unanimity on the age of onset of enuresis and the different frequency criteria used. It is likely that a definition of bedwetting at least once monthly as used partly in this study and by some workers[3,4] may overestimate the problem in children less than six years of age. The reverse may be the case in the older age group when at least, two times weekly as used by some other workers[4,5] is used to define nocturnal enuresis. The definition used in the present study is graded taking age into consideration.

Although the definition and aetiology of nocturnal enuresis have not been clarified or established, it is believed to be multifactorial.[8] As such, it would be difficult to explain the gender difference noted in the children with SCA in some studies.[3,5] In the present study significantly more male than female controls were affected, no gender difference was noted in the prevalence of nocturnal enuresis in children with SCD-SS.. It is possible that whatever the underlying causes of nocturnal enuresis are in the normal population, they are probably also operational in SCD-SS children. In addition, children with SCD-SS have been shown to have a near total destruction of their renal medullary vasa recta.[2] This will impair their ability to adequately concentrate their urine and also lead to production and excretion of a larger than usual amount of urine.[2] Children with SCA have a mean urinary output that is 53 percent greater than that of children with normal haemoglobin.[9] This additional factor may explain the greater prevalence of enuresis in these children compared to the normal population and probably obliterate any tendency towards gender differences in prevalence.

A maturational lag has been suggested as a cause of nocturnal enuresis. This is likely to be a factor in sickle cell anaemia-related nocturnal enuresis. Delay in pubertal changes is known in SCA. This may be

related to SCA-related damage to the central nervous system.[12] In the present study, SCD-SS children started walking at a significantly older age compared to controls and motor achievement is known to correlate with appropriate myelinization and brain growth.[13] Unlike what was observed in an earlier study,[4] we were unable to demonstrate any relationship between the prevalence of nocturnal enuresis and family size or type in either group of children. Even though most home caregivers of enuretic SCD-SS children think of the condition as not being abnormal, the methods employed in response to nocturnal enuresis may be harmful to them. Withholding fluids in hyposthenuric SCD-SS children, for instance, may rapidly lead to significant dehydration with dire consequences. Scolding and/or spanking may add to the psychological burden already being experienced by these children.[14]

Only three families in this study sought any health advice. None used medically prescribed medication, while nine (2.1 percent) children received home-prescribed unspecified medication. Similar poor performances have been reported with only about one-third of families seeking medical advice[5,7] and only one percent using prescribed medications.[5] It is likely that as had been shown previously, many home caregivers in the present study may not see nocturnal enuresis as a health problem to be handled in the hospital setting.[10] The fear of social and emotional stigma to the family and index child may be another reason for not seeking medical advice.[8,11]

We concur with the view that enuresis is more common in SCD-SS than in the normal population, that it is multifactorial in origin, and that it is being under-reported. We do not think nocturnal enuresis is innocuous in SCD-SS as is the case in control children. It is suggested that efforts be intensified to establish its aetiology and significance in sickle cell anaemia.

Acknowledgments

We thank the consultants in the Department who allowed us access to their patients that were used as controls. We also appreciate Prof. AM Yakubu's efforts in kindly but critically revieweing the script.

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Table II

Presenting Symptoms of Cardiac Disease in 49 Children

Symptom	*Number of Patients*	*% of Total*
Difficulty in breathing	30	61.2
Fatigue	22	44.9
Fast breathing	20	40.8
Dark lips	15	30.6
Poor feeding	11	22.4
Excessive sweating	9	18.4
Palpitations	3	6.1
Chest pain	3	6.1

Table III

Presenting Signs of Cardiac Disease in 49 Patients

Signs	*Number of Patients*	*% of Total*
Cyanosis	5	10.2
Finger clubbing	5	10.2
Chest deformity	5	10.2
Polycythemia	5	10.2
Murmurs	46	93.9

Table 1V

Types of Cardiac Disease by Clinical Diagnosis

Type	*Male*	*Female*	*Total*	*Percentage*
VSD	10	8	18	36.7
RHD	5	7	12	24.5
Tetralogy of Fallot	8	2	10	20.4
Syncope/Arrhythmias	2	3	5	10.2
PDA	2	0	2	4.1
ASD	2	0	2	4.1
Total	29	20	49	100

RHD = Rheumatic heart disease

Table V

Cardiac Diseases Diagnosed by ECHO in 19 Patients

Type	*Male*	*Female*	*Total*	*Percentage*
Isolated VSD	2	2	4	21.1
Tetralogy of Fallot	3	1	4	21.1
PDA	1	0	1	5.26
ASD +VSD	0	1	1	5.26
VSD +PDA	1	1	2	10.5
RHD	1	2	3	15.8
Arrhythmias	1	0	1	5.26
Cardiomyopathy	1	0	1	5.26
PS + PFO	1	0	1	5.26
DORV	0	1	1	5.26
Total	11	8	19	100

DORV = Double outlet right ventricle

Fallot, PDA, rheumatic heart disease (RHD) and arrhythmias were correctly diagnosed. However, DORV was wrongly diagnosed as a large VSD with pulmonary obstructive vascular disease (POVD), PS + PFO as a VSD and the child with cardiomyopathy as having RHD. The two patients who had combined lesions of VSD +PDA and VSD + ASD were each diagnosed as a case of a large VSD. In all, there was 68.4 percent accuracy (13/19) between the clinical and echo diagnoses.

Six (31.6 percent) of the patients who had echo confirmed diagnosis have had surgery. The patients with DORV+PS, VSD+ASD, PS+PFO and Tetralogy of Fallot respectively, had surgery in India, One patient with VSD+PDA had surgery in Israel while one with Down's syndrome and ASD+VSD had surgery in America. Seven (14.3 percent) of the patients have died while 12 (24.5 percent) were lost to follow-up. All the patients who had surgery except two, are seen regularly in the clinic. One died one month after intra-cardiac repair (ICR) for Tetralogy of Fallot while riding on his bike while the second had successful surgery but had not returned to the country. The remaining 24 (59 percent) patients awaiting financial assistance for surgery are being stabilised on appropriate medical management meanwhile.

Discussion

Heart diseases constitute a major cause of childhood morbidity and mortality in Nigeria[8] and is among the top 10 non-communicable diseases according to recent studies in the country.[9,10] The incidence is largely unknown because of absence of large multi-centre studies. However, it is estimated to be high because of the high incidence of rheumatic fever in many developing countries.[11] The male preponderance in this series is similar to those reported from Nigeria[12] and other countries.[13,14] The finding that VSD was the commonest lesion seen, accounting for 36.5 percent of the cardiac disease, is similar to those reported in two other echocardiological studies reported from Nigeria in which VSD accounted for 37.5 percent[15] and 30.8 percent[12] of cases respectively, and was thus the commonest lesion encountered. The natural history and clinical course of VSD were explained to parents depending on the timing and severity of presentation since effective size of the VSD was not determined. Patients presenting in heart failure in early infancy were unlikely to have spontaneous closure. The four cases of isolated VSD who benefited from echo diagnosis in Ibadan had been correctly diagnosed without echo, while two others who were thought to have isolated VSD were

subsequently found by echo to have associated ASD and PDA.

Tetralogy of Fallot (TOF) accounted for 20.4 percent of cases diagnosed, and was the only cyanotic CHD detected in this study. The incidence was higher than the 17.1 percent[12] and 15 percent[15] recorded in northern Nigeria, probably because other causes of cyanosis such as hypoplastic left heart syndrome and TGA might have been missed and diagnosed as TOF. The importance of echocardiography in differentiating TOF from other cyanotic CHD cannot be overemphasised.[15] It is gratifying to note that the four patients who were diagnosed at Ibadan had earlier been correctly diagnosed without echo in our centre. Patients with rheumatic heart disease accounted for 24 percent of all cases. This was less than 29.5 percent[12] and 39.5 percent[15] reported earlier, probably because other reports were based on echo findings with better view of valvular involvement. However, rheumatic heart disease is still a major public health problem in Nigeria due to poor living conditions, and inadequate health care, among others. It is known to be a sequel of acute rheumatic fever which is controllable by improved living conditions and prompt and adequate treatment of sore throat.[12] It is noteworthy that 60 percent of the 19 patients who could afford echo evaluation in Ibadan were males. This is expected in this country where male preference is still high.[16]

The 68 percent accuracy of our clinical diagnosis in this study is noteworthy considering the absence of formal training in Paediatric Cardiology. This report highlights the fact that, in the absence of special tools in evaluating cardiac patients, the age long practice of history taking, physical examination and chest radiography still play a major role in effective diagnosis. Many centres in Nigeria do not and may not have such relatively sophisticated equipment for the foreseeable future because of the exorbitant cost of the machine. Even if the equipment is available, personnel will still need to be adequately trained in its use. The onus then is on the paediatrician to make the best use of the readily available methods. Referral to other centres with trained cardiologists and modern equipment is encouraged for patients who can afford it.

Conclusion

History and clinical examination remain the mainstay in the diagnosis of cardiac disease in the absence of specialised tools such as an echocardiogram. These are essential pre-requisites before a meaningful echo can be done. Training of Fellows in paediatric cardiology and adequate equipping of Federal and State government hospitals is an urgent necessity. The Federal Government should complement the efforts of non-governmental organisations like the Save a Child's Heart Nigeria while plans should be expedited to set up at least, two cardiac centres in the country.

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