

Nocturnal Enuresis in Children and Adolescent with Sickle cell Anemia

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Abstract

Children with sickle cell anemia (SCA) have a tendency to have nocturnal enuresis (NE) more than normal children with males being more affected than females. Mechanisms of NE that operate in normal children probably do so in children with SCA. Postulated causes of nocturnal enuresis in individuals with SCA include hyposthenuria causing nocturnal polyuria, reduced bladder capacity or nocturnal bladder overactivity, sleep disordered breathing and an increased arousal thresholds. The variation in the reported prevalence rate of NE in SCA is probably due to differences in definition criteria and methodology. This review will discuss the prevalence rate and postulated causes of NE in children with SCA.

Keywords: Sickle cell anemia; Nocturnal enuresis; Prevalence; Pathogenesis; Hyposthenuria; Obstructive sleep apnea; Periodic limb movement syndrome; Restless leg syndrome; Vitamins

replaced by valine in the 6th position of the beta chain. This causes polymerization of hemoglobin S in low oxygen tension leading to episodic occlusion of microcirculation [1].

Introduction

Sickle cell anemia (SCA) is one of the most common genetic disorders characterized by single gene mutation, where glutamic acid is

Study/year	Study design	No(age range)	Prevalence%	Prevalence males/ females (%)	Primary NE%	Secondary NE
Barakat et al. [6]	Prospective structured phone interview. USA	217(5-22) Hb SS	20	28.1/11%	----	
Jordan et al. [7]	Prospective interview +symptoms check list. USA	126 (5–17) Hb SS	25	Not reported		
Ekinci et al. [8]	Prospective questionnaire (Turkey)	55 (Hb SS (6–40)	9.1%	Not reported	----	
Chakravorty S et al. [9]	Cross-sectional, questionnaire base interview UK	43(HbSS) AGE:6-17 yrs	(30.2%)	37.9/33.3%		
Eneh et al. [10]	Prospective cross-sectional descriptive	70(5-11) Hb SS	31.4	48.7%/9.7%(p<0.0001	Not determined	
Ahmed et al. [11]	Prospective cross-sectional(Sudan	78(5-16) Hb SS	37.9	64% with ne were males	84.8	15.2
Eneh et al. [12]	Prospective	70(8.37 ± 2.02) Hb SS	31.4	48.7/23.1	Not determined	

Table 1a: Studies that used DSM-1V criteria to define nocturnal enuresis.

Study/year	Study design	No(age range)	Prevalence%	Prevalence females (%)	males/	Primary NE%	Secondary NE
Readett et al. [13]*		175 (Hb SS)	45.1% 15.1%	52/38(NS)			
Figueroa et al. [14]*	Prospective screening questionnaire (USA)	91 (6–21) HB SS, HB ßS	30%	Not reported			
Ogunrinde et al. [15]**	Structured questionnaire	360(5-17) HB SS	41.7	46.7/36.4		75.5	

*- Studies that used frequency definition; **- Studies that used duration definition.

Table 1b: Studies that used incomplete DSM-IV criteria for definition of nocturnal enuresis.

Study/year	Study design	No(age range) /genotype	Prevalence%	Prevalence males/ females (%)	Primary NE%	Secondary NE
Suster et al. [4]	Parents interview	29(4-12) Hb SS	68.9	Not reported		
Akinyanju et al. [16]	Parental interview. Nigeria	206(4-20)	36.8	2.6:1		
Mabiala, et al [17]	Cross sectional	456 (5-20) Hb SS	50.9	Common in females		
Field J et al [18]	Prospective infants cohort	213(6-20) Hb SS	33 %	Not reported	Not determined	Not determined
Portocarrero et al. [19]	Prospective	155(5-17) Hb SS	32.2	39%/20%	86%	14%
Lehman et al. [20]	Prospective	221(4-19) Hb SS	39.9	48.6%/29.4%		
Mbong et al. [21]	Case control	45(2-17) Hb SS	56.8	54.5/21.7		
Rosen CL [22]	Prospective	243(4-18) 231 Hb S 12 HbSß0	30%	-	Not determined	Not determined
Al-Otaibi T [23]	prospective	65(2-14) HB SS	46%	-	-	-
Daniel LC [24]	prospective cross-section	54(4-10) Hb SS	37%			
Jane S. Hankins [25]		100(2-18) Hb SS	24			

Table 1c: Studies that used other definitions.

SCA is a worldwide disease that affects mainly African, black-American, Arabs and those of Asian ancestry [2]. Wetting the bed at night two or more times per week after age 5 years, for a period of at least 3 months is called nocturnal enuresis (NE) [3]. NE is classified into primary (never being dry) and secondary (was dry before) enuresis and divided further into monosymptomatic (without daytime symptoms) versus non-monosymptomatic (with daytime symptoms) enuresis.

Prevalence of Nocturnal Enuresis in SCA

The first report on the prevalence rate of NE in SCA was in 1967 by Suster and Oski who reported a prevalence rate of 68.9% [4]. In 2014 Wolf and colleagues in a review article estimated the prevalence rate of NE in children and adolescent with SCA to range from 9-51% and that was derived from 10 relevant studies [5]. In this review 21 articles that reported the prevalence rate of NE in children and young adults with

SCA were retrieved after thorough literature search (Table 1A-1C) [4,6-25]. We categorized these articles in 3 groups according to the criteria used to define NE.

Group 1(Table 1a): Studies (total 7) that used Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria for the diagnosis of NE.

Barakat et al. [6] studied 217 patients 5-22 years old and NE was reported to be present in 20% of them [6]. Ekinci et al. [8] from Turkey studied a mixed population of thalassemia and sickle cell anemia 6-40 years old. Out of 55 patients with sickle cell anemia only 5 patients (9.1%) were enuretic and they were children 11.0 ± 2.82 years old [8].

The remaining 5 studies included children whose ages were 5-17 years old, with a variation in age range, reported a prevalence rate of 25-37.9% [7,9-12].

Group 2(Table 1b): A prevalence rate of 30-45.2% was reported by the studies that used incomplete DSM-IV criteria to define NE [13-15].

Group 3(Table 1c): These are the studies that used different diagnostic criteria, they reported a prevalence rate of 32.2%-68.9% [4,16-25].

Primary nocturnal enuresis was the comments reported type, it occurred in 75.5-86% of patients [11,15,19]. This is similar to what had been reported in normal children with NE [26-28]. Only two studies further divided NE into monosymptomatic (MNE) and nonmonosymptomatic(NMNE) [9,19]. MNE was reported in 42-48.2% and NMNE was present in 51.8%-58% of children with NE.

The prevalence rate of NE in children with SCA decreases with increasing age from 29.7% at age 4-8 years to 9% at age 18-20 years (Figure 1) [6,9,10,12,16,17,19,20]. A similar trend was also observed in enuretic normal children [26-30].

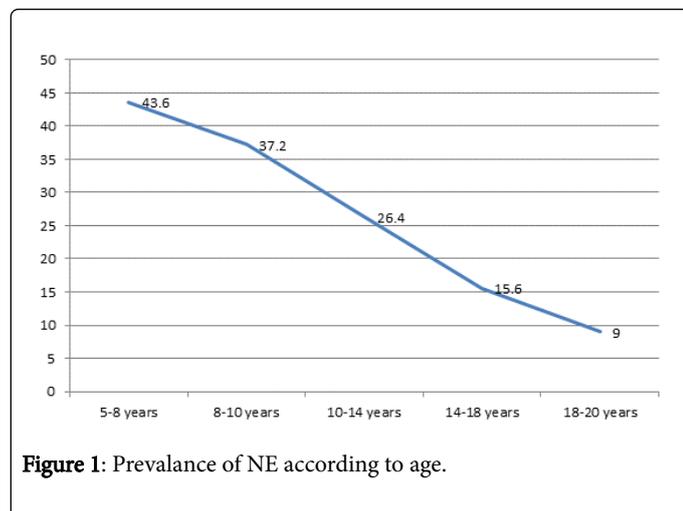


Figure 1: Prevalance of NE according to age.

The effect of gender on the prevalence rate of NE was reported by 12 studies. Boys were reported by 10 studies to have higher prevalence rate than girls [6,9-12,15,16,19-21], equal rates in both sexes was reported by one study [13] and one study reported a higher rate in females [17]. These findings are similar to those reported in normal children with NE [28,30-35]. According to Bottomley et al. [36] NE in normal children is twice more common in boys than girls up to the age of nine years, but thereafter there is no gender difference in prevalence [36]. No such observation was reported in children with SCA.

Enuresis in SCA: the postulated etiology

Wolf et al. in their review suggested that NE in SCA may be due to etiopathological factors that cause enuresis in normal children, SCA-related factors or a combination of both [4] The contribution of each of these factors in the causation of NE is not yet known.

The role of hyposthenuria in SCA-related nocturnal enuresis

The occurrence of hyposthenuria in patients with sickle cell anemia has been noted since 1928 [37]. Old studies had shown that all patients with SCA and about 70% of patients with sickle cell trait (SCT) have failure to maximally concentrate urine irrespective of age [38,39]. In two third of patients with SCT the defect in maximum urine concentration was similar to that seen in those with SCA [38]. The maximum urinary concentration declines with age in SCA and SCT [39]. Subsequent studies, using urine specific gravity or urine osmolality, demonstrated hyposthenuria in SCA and SCT as well [40-42].

The first study that linked hyposthenuria and nocturnal enuresis was in 1967 by Noll et al. [43]. This assumption was based on the fact that failure to concentrate urine is one of the earliest infarction- related renal complication of SCA [44]. Hyposthenuria, was therefore plausibly thought to manifest as polyuria and enuresis [45-47]. Subsequent studies did not support this assumption.

Readett et al. in 1990 investigated 16 enuretic and 16 age and sex matched non-enuretic children with SCA. There was no significant difference in maximum urine osmolality or urine volumes in the two groups following an overnight fluid deprivation tests N [48]. Ahmed et al. [11] in 2016 studied 87 children with SCA, 53 children with sickle cell trait and 50 normal children as a control. The mean urine specific gravity (USG) was within the normal range in the three groups. Furthermore, the mean urine specific gravity was 1.025 in sickle cell anemia patients with enuresis compared to a mean urine specific gravity of 1.027 in the sickle cell anemia patients without enuresis (P o. 15). In addition to that the prevalence rate of NE in children with sickle cell trait was not different from the control group (13.2% vs. 12.0% P 0.61). Eneh et al. in 2017 [12] studied 70 children with SCA and 70 children as control. The mean USG was significantly higher in the study group than in the control (1.02 ± 0.01 vs. 1.01 ± 0.01 , P 0.018) Hyposthenuria was present in 4.5% of enuretic children with SCA compared to 8.3% of nonenuretic SCA patients. Furthermore they found that the mean USG was significantly higher in enuretic children with SCA compared to enuretic control (1.02 ± 0.01 vs. 1.01 ± 0.01 , P 0.0107). How many children developed enuresis among those with hyposthenuria in both groups was not determined [12].

Figuroa et al. treated 10 children with SCA and enuresis with intranasal desmopressin acetate, 4 patients showed complete response and partial response was observed in other 2 patients [49]. Although the number of patients was small, the response rate to treatment is comparable to that seen in normal children treated with desmopressin for nocturnal enuresis [50]. From what had been mentioned above hposthenuria does not appear to be the root cause on NE in patients with SCA. In addition these findings support the concept that NE in SCA, although the prevalence is increased, has causes and treatment similar to normal children [60].

The urinary bladder and nocturnal enuresis

In children with SCA the maximum functional bladder capacity was found to be significantly decreased in enuretic children compared to nonenuric group and the ratio of overnight urine volume to maximum functional bladder capacity was significantly increased. Thus nocturnal enuresis was attributed to diminished bladder capacity [48].

Strong association between NE and urinary bladder dysfunction (UBD) was reported in children and adults with SCA [6,14,19,47,48,51,52]. Enuresis and nocturia, as indicators of UBD, are common in individuals with sickle cell anemia [18,43,53,54]. Field et al. reported that enuresis declined with age but nocturia persisted throughout childhood and early adulthood [18]. They attributed the reduction of NE despite the persistence of nocturia to improvement of sleep arousal in those patients. An increase in the maximum functional bladder capacity with age could be another possible explanation [50-55]. In a recent report, Claudino et al. [56] evaluated the urinary bladder function in a transgenic Sickle Cell Disease Mice. They found the following; reduced urine output, incapacity to produce typical bladder contraction and bladder emptying, lower detrusor muscle relaxation, small bladder contraction and reduced urethral contraction. Histologically there was reduction in detrusor muscle thickness and bladder volume in addition to chronic inflammatory cells infiltrates. They attributed these findings to chronic bladder ischemia resulting from repeated cycles of ischemia-reperfusion injury caused by SCA vasocclusion. The authors stated that the atonic detrusor muscle causes an underactive bladder with impaired bladder emptying and the reduction in the contractile response of the urethra leads to impaired continence which may contribute to enuresis observed in patients with SCA.

NE and Sleep-related disorders in SCA

These are conditions that cause poor quality or insufficient amount of sleep. They include among others sleep-disordered breathing (SDB) [like obstructive sleep apnea (OSA)], restless legs syndrome (RLS) and periodic limb movement syndrome (PLMS) [25].

Night waking and sleep-disordered breathing was commoner in children with SCA than the control [25]. Obstructive sleep apnea (OSA) is the commonest of these disorders [57]. Few studies have described sleep-disordered breathing and OSA in children and adolescent with SCA using polysomnography (PSG) [23,58-62]. OSA was reported in 10-80% of children with Sickle cell disease [58-62,23]. A prevalence rate of 0.7-3% was reported in normal children [63].

NE and upper airway obstruction are they related?

A high prevalence rate of NE was found in normal children with upper airway obstruction [64-66]. A prevalence rate of 8-47% of NE was reported by some studies [66-70] in comparison to a prevalence rate of 2-15% in children without upper airway obstruction [71-74]. A high resolution rate of childhood nocturnal enuresis has been associated with tonsillectomy and/or adenotonsillectomy [64,66,75-83]. Moreover, nocturnal enuresis resolved in two children with mild obstructive SDB following administration of nasal corticosteroids [84]. Mbong et al. [21] reported a prevalence rate of NE of 100% in children with SCA and OSA compared to 46.2% in those without OSA ($P = 0.004$). In a recent study from Saudi Arabia NE was reported in 62% of children with SCA and Obstructive apnea-hypopnea index (OAHI) ≥ 1 compared to an overall prevalence rate of 46% [23]. Lehman and colleagues demonstrated in their study that

habitual snoring and SDB with and without habitual snoring are associated with enuresis in children with SCA. The presence of enuresis, after adjusting for age and gender, was associated with OAHI ≥ 2 (OR 2.19; 95% CI 1.09, 4.40; $p = 0.03$). After adjusting for age and gender, the association of habitual snoring alone and severe enuresis (≥ 3 wetting per night) among children with SCA was statistically significant (OR 1.83; 95% CI 1.02, 3.29; $p = 0.043$) [20]. The authors suggested that in an enuretic child with SCA and snoring with adenotonsillar hypertrophy a formal sleep test should be performed; if SDB is detected then adenotonsillectomy would be the next line of therapy as recommended by the American academy of pediatrics [85]. The effect of tonsillectomy and/or adenotonsillectomy on NE in children with SCA and OSA was not studied.

Why does enuresis increase in children with OSA?

Among other factors [86-90] an increased bladder pressure as a result of increased abdominal pressure that occurs when breathing against an obstructed airway was suggested as a pathogenesis of NE. The increased bladder pressure in addition to the reduced urethral contraction that was observed in the transgenic Sickle Cell Disease Mice [56] could explain the increased frequency of NE in children with SCA and OSA.

Periodic limb movement syndrome (PLMS) and restless leg syndrome

Periodic limb movements are repetitive, highly stereotyped movements of the arms or legs occurring during sleep [91]. It is not commonly studied in children with SCA. It was reported in few studies to occur in 20.5-29% of children with SCA [25,59,93], a prevalence significantly higher than a 1.2-8% rate reported in healthy children [92-95]. RLS was reported in 11.1% of patients with SCA [25]. 12% of children with SCA who had PLMS had RLS [93]. Both PLMS and RLS were associated with sleep disruption [93]. Dhondt et al. studied 67 normal children with NE and 67 as a control for PLMS. Children with NE were found to have higher incidence of periodic limb movement and sleep fragmentation [96]. An increased occurrence of night waking and enuresis was observed in children with SCA [24]. Since patients with SCA have higher rate of PLMS which is associated with NE and sleep disruption we expect these children to have a high prevalence rate of NE. Research in this area is needed.

Brain maturation and nocturnal enuresis in SCA

Disorder of maturation of the brain, lack of arousal and a deficit in inhibition of micturition reflex have been considered to be the main abnormality leading to nocturnal enuresis in normal children. The markers reported to indicate cortical and brain stem immaturity were the presence of delayed bone age [97, 98] slower motor performance [99] and reduced activation during motor response inhibition in children with PNE. Using functional magnetic resonance imaging (fMRI) of the brain, a relative lack of or delay in the maturation of prefrontal cortex circuitry, known to suppress inappropriate responses, was demonstrated by one study [100]. Another marker was the microstructural changes that were found in the brains of children with monosymptomatic NE. These abnormalities were located in the thalamus, frontal lobe, anterior cingulate cortex and insula [101]. Adults patients with schizophrenia who had NE in their childhood were found to have significant reduction in the brain gray matter involving the frontal and parietal lobes [102]. Further evidences were derived from neurophysiological studies [103-105]. The anatomical

and physiological abnormalities were observed in areas which are involved in arousal and micturition control. There are no similar neurophysiological studies in children with SCA and NE but there was one study that used electroencephalogram (EEG) in subjects with SCA and showed generalized slow wave activity and that was suggested to be partly due to delayed brain maturity [106]. Various brain injuries were described in children with SCA. A significant reduction of the grey matter involving the cortex, thalamus and caudate nucleus was reported [107]. Using a quantitative MRI increased T1 was observed in the thalamus, frontal white matter, genu, and occipital white matter [108]. Regional cortical thinning particularly involving the precuneus and the posterior cingulate was described [109]. This regional cortical thinning was found to be associated with reduced cerebrovascular reserve especially in areas with high metabolic activity (anterior cingulate, posterior cingulate, occipital gyrus, precuneus) [110]. Microstructural abnormalities of cerebral cortex, frontal white matter, centrum semiovale, periventricular areas, head of the caudate nucleus, thalamus, brainstem, and pons were demonstrated by Balci et al. using quantitative brain diffusion-tensor MRI [111]. A progressive loss of brain volume [112] and volumetric growth delay of the brain gray matter was also demonstrated in these children [113]. Ischemia and/or infarction especially of the thalamus and basal ganglia were also described [114,115].

The micturition control network is widely spread in the brain. In their review article of published reports of brain imaging relevant to normal urine storage Griffith et al. found that sensation of urine storage is mapped in the insula; the anterior cingulate gyrus provides monitoring and control; the prefrontal cortex (PFC) makes voiding decision [116]. PFC was found to be under activated in normal children with primary NE, a finding suggestive of its immaturity [100]. The areas responsible of micturition control are part of the injured areas in patients with SCA and that might affect all aspects of micturition predisposing these children to NE among other voiding dysfunction.

It is interesting to note that children and adolescent with attention-deficit/hyperactivity disorder (ADHD), like those with SCA, have shown significant reduction in brain volume, gray matter volume and cortical thickness [117]. ADHD which is strongly associated with NE [118] was reported to occur in 19-25% of children with SCA [119].

Nocturnal enuresis and vitamins

Vitamin B12 and folate levels were reported to be low in normal children with primary nocturnal enuresis. Altunoluk et al. studied 30 children with Primary nocturnal enuresis, their mean serum B12 level were significantly lower compared to the control group; 30% of enuretic patients were found to have vitamin B12 deficiency but none of the control group [120]. Another study from Pakistan had shown lower level of serum B12 and folate in children with enuresis compared to non-enuretic children but none of the patients were deficient [121]. The authors suggested that this association might be due to delayed maturation of the brain as a result of low level of these vitamins.

Low level of vitamin B12 was reported in patients with SCA. Al-Momen reported vitamin B12 deficiency in 43.5% of patients with SCA age 14-49 years [122]. In Sudanese children with SCA age 6 months-15 years Vitamin B12 level was found to be significantly lower than the control and 7.1% were found to be deficient [123]. Similar results were reported by other studies [124-127]. 15% of children with sickle cell anemia had low serum folate despite adequate supplementation [127].

Wide spread microstructural changes in the cerebral white matter [128] and an altered cerebral blood flow [129] was demonstrated in adults with vitamin B12 deficiency. The altered cerebral blood flow was reversed with vitamin B12 treatment [129]. The effects of vitamin B12 on the brain are suggested to be mediated by the altered methylation reaction [130]. The current literature suggested a relationship between vitamin B12 and gray matter damage. People with good intake of vitamin B12 have a greater volume in the left and right superior parietal sulcus [131] and B-vitamin treatment markedly reduces gray matter atrophy in certain areas in the brain [132]. There are no studies that report vitamin B12 level in children with SCA and NE. Also there are no studies that looked at the brain microstructure of children with low level of vitamin B12. Studies are required to explore this area.

Vitamin D

Defining deficiency as vitamin D < 20 ng/ml, low 25-hydroxy [25(OH)] vitamin D was found to be associated with an increased risk of NE in children aged five to seven years. Furthermore, the severity of NE increases as the level of 25(OH) D decreases [133]. Using the same definition in a systematic analysis, the prevalence of vitamin D deficiency was reported to range from 56.4 to 96.4% in children with SCA [134]. The association between vitamin D deficiency and NE can be explained partly by its influence on SDB and nocturnal polyuria.

Low level of serum 25(OH) D was reported to increase the risk of developing OSAS [135-137] and primary snoring [138]. Persistent low level of vitamin D may also increase the risk for obstructive sleep apnea by promoting adenotonsillar hypertrophy, chronic rhinitis and/or airway muscle myopathy [137, 139].

Restless leg syndrome (RLS), another SDB, was found to be more frequent and more severe in adults with vitamin D deficiency [140-142] and it has a negative effect on sleep parameters [8]. Vitamin D supplementation was found to improve the severity of RLS [143]. The association of OSAS and RLS with NE in children with SCA was discussed earlier.

Vitamin D receptors were reported to be present in the brain in areas that have an important role in initiation and maintenance of sleep [144]. Moreover significant improvement in sleep quality was observed with vitamin D supplementation [145]. Vitamin D deficiency in children and an adolescent with SCA was associated with painful crisis [146]. Pain literature had shown that nocturnal pain disturbed sleep [147]. A subjective sleepiness can accompany the relative elevation of the levels of inflammatory mediators as part of immune dysregulation that is proposed to occur with low 25(OH) D [148]. Children with NE were observed to suffer from sleep fragmentation [149]. Therefore, it is plausible to assume that low vitamin D is associated with poor sleep quality including sleep fragmentation in children with SCA that leads to NE.

Vitamin D receptor knockout mice that had normal renal function were observed to develop polyuria, as a result of increased water intake [150]. The latter was due to renin up regulation leading to an increased production of angiotensin II [151]. In another study, using similar mice, reduction of renin-angiotensin activity in paraventricular nucleus with inhibition of thirst was achieved following vitamin D analogs injection. The authors concluded that polydipsia and polyuria may be caused by a lack of vitamin D [150]. Nocturnal polyuria had been reported in normal children [152,153] and children with SCA who had NE and was considered a pathogenic factor [18,41,51,52]. In

conclusion low vitamin D level may lead to NE through OSA, sleep fragmentation and nocturnal polyuria.

Cortical arousal and NE in SCA

Impaired cortical arousal, as determined by known EEG parameters, is a probable risk factor for NE. Children with NE were considered deep sleepers [154]. There are conflicting data regarding the pattern of sleep in children with NE [155,156]. Frequent cortical arousal with inability to awaken completely was observed in children with severe refractory NE [157]. Pattern of cortical arousal has not yet been assessed in children with SCA and NE. Sleep architecture of children and adolescent with SCA was found to be similar to that of normal children [158]. High rates of SDB and night waking was reported in children with SCA [159]. Sleep fragmentation is a common features in children with SCA and PLMS and RLS [93,96]. Thus repeated cortical arousal might be common in SCA and NE. Studies are needed to explore this area.

Conclusion

NE is prevalent in children with SCA; it occurred in 25-37.9% of them according to DSM-IV criteria. Males are commonly affected. Primaty NE is the commonest type. Nocturnal and diurnal enuresis occurs at almost equal rates. NE is likely to be due to multiple causes. Sleep-related disorder is associated with increased prevalence of enuresis. Hyposthenuria is not the root cause of NE. Low levels of cobalamine and vitamin D are theoretically probable modifiable cause of NE. Further studies are needed to explore this area.

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