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Characteristics of symptoms of imminent eclampsia: A case referent study from a tertiary hospital in Tanzania

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ABSTRACT

Background: Maternal mortality in developing countries is unacceptably high with eclampsia being consistently among the top causes. As yet, primary prevention of this complication is not possible since causes of pre-eclampsia are largely unknown and biochemical, hematological and radiological markers have proved unsuitable for routine prediction of eclamptic fits. Although headache, visual disturbance, abdominal pain, nausea, and vomiting are routinely elicited when managing pre-eclampsia and have been reported to predict eclamptic fits, the literature attempting to characterize them is scanty. We sought to establish characteristics of the prodromal symptoms of eclampsia and compare them with similar symptoms as experienced by normotensive pregnant women at Muhimbili National Hospital (MNH) in Tanzania. Methods: This study was conducted at MNH in 2010 by enrolling 123 eclamptic and 123 normotensive women. Women in the two groups were interviewed about their experiences and characteristics of headache, visual disturbances, abdominal pain, nausea and vomiting using a semi structured questionnaire. The severity, nature and other characteristics of the symptoms were assessed using standard scale/methods and data compared among the two groups. Results: Prodromal symptoms of eclampsia were present in 90% of eclamptic women. Headache was more frequent among eclamptic women (88%) than the normotensive (43%), $p < 0.001$). The symptom was also more perceived as severe among eclamptic (46.3%) than the normotensive (5.7%), $p < 0.001$. The most frequent location for headache was frontal in 65.7% of eclamptic women compared to frontal (41.5%) or generalized (39.6%) for the normotensive. Likewise, visual problems were significantly more frequent among eclamptic women (39%) compared to the normotensive (3%), $p < 0.001$. Upper abdominal pain was significantly more reported by eclamptic (36%) than normotensive women (0.9%), $p = 0.001$. The general occurrence of abdominal pain, nausea and vomiting was not significantly different in the two groups. The time lag from development of a symptom to eclamptic fit was up to seven days for most symptoms except visual disturbances of which 98% developed fits within 12 hours. Conclusion: Whereas the prodromal symptoms of eclampsia and similar symptoms in normotensive women were common, the characteristics of headache and visual disturbance differ significantly in the two groups. The knowledge of these differences could be utilized to improve the quality of management of pre-eclamptic women in order to prevent eclampsia.

Keywords: Eclampsia; Symptoms; Headache; Blurring of Vision; Abdominal Pain; Tanzania

1. INTRODUCTION

Pre-eclampsia (PE) is a multisystem hypertensive disorder of unknown cause that is unique to human pregnancy. It is characterized by abnormal vascular response following placentation that leads to functional changes such as increased systemic vascular resistance, enhanced platelet aggregation, activation of coagulation system and endothelial cell dysfunction [1,2].

Symptoms that accompany pre-eclampsia are a result of generalized vasospasms, fibrin and platelet deposition and occlusion of blood flow to vital organs. In severe cases the liver is affected where sub capsular haemorrhage, necrosis and edema of the liver cell occurs producing epigastric pain and impaired liver function [3]. The brain becomes edematous and this in conjunction with vasospasm hypertension and disseminated intravascular coagulation (DIC) can produce cerebral under perfusion, ischaemia, and necrosis of blood vessel resulting in headaches, visual disturbances and cerebrovascular accident [4,5].

Pre-eclampsia affects 5% to 10% of all pregnancies and is not confined to any population group [6,7]. Globally eclampsia accounts for 12% maternal mortality

mostly in the developing countries where the incidence of eclampsia is high and quality of care of pre-eclamptic women is low [8-13]. The case fatality rate for clampsia is less than 1% in many developed countries and generally above 5% in developing countries [7,9-12].

The exact incidence of eclampsia in Tanzania is unknown and the few available data are hospital based. An estimated 67 cases of eclampsia occur per 10,000 births in Dar es Salaam community [14]. At Muhimbili National Hospital (MNH) where eclampsia is among the top two causes of maternal mortality the incidence of eclampsia ranges from 200 - 504 per 10,000 births with a case fatality rate of about 5% [14-16].

In spite of intense basic research, the etiology and pathophysiology of pre-eclampsia and eclampsia is still not fully understood [17,18]. Currently there are no reliable methods suitable for routine screening for both pre-eclampsia and eclampsia, hence primary prevention of pre-eclampsia is not possible. The validity of biochemical, hematological and radiological markers to predict eclampsia has been practically insufficient to recommend their routine use [13,18-23]. The absence of clear diagnostic markers to predict the risk of progression from pre-eclampsia into eclampsia has made researchers to investigate symptoms that can be used to predict the onset of eclampsia [21,24-26].

Headaches and visual symptoms, epigastric abdominal pain, nausea and vomiting have been consistently reported as important premonitory symptoms for eclamptic fits [24-26]. One systematic review has recently reported the usefulness of these symptoms in predicting complications of pre-eclampsia compared with when they are not present [21,25], but others have cautioned on the reliance on such routine risk factors to predict maternal outcomes [27]. Although these symptoms are routinely elicited when managing pre-eclampsia patients, they are poorly defined. The few studies that have attempted to investigate premonitory symptoms have neither included detailed descriptions of the individual symptoms nor compared them with similar complaints in normotensive pregnant women [24]. Moreover, it is well known that the occurrence of neurological symptoms such as headache and gastrointestinal symptoms of nausea and vomiting may be exaggerated in normal pregnancy due to physiological changes [28-31]. Furthermore, in the tropics such symptoms might be confused with symptoms due to parasitic infections such as malaria of which pregnant mothers tend to be vulnerable [8,31]. Given this background the current study was designed in order to determine distinguishing clinical features of the prodromal symptoms of eclampsia. Our results were expected to contribute to improvement in the recognition and management of severe pre-eclampsia and prevention of eclampsia.

2. METHODS

2.1. Study Settings

This hospital based case referent study was conducted from April to August 2010 at MNH in Dar es Salaam, Tanzania. MNH is one of the four referral hospitals in Tanzania. It offers specialized obstetric services for Dar es Salaam city which is the biggest in Tanzania, and its suburbs. The city of Dar es salaam is estimated to have a population of 3.4 million people according to the 2002 national population census with an annual growth rate of 4.3%. There are 3 districts in Dar es Salaam; Ilala, Temeke and Kinondoni. Each district has a district hospital which provides emergency obstetric care. However most of obstetric emergencies in Dar es Salaam are referred to MNH. In addition patients are also referred from nearby regions. Apart from the referred patients, a substantial number of patients with or without obstetric complication come directly from home.

2.2. Study Sample

For the cases, the population constituted eclamptic women admitted in ICU at MNH with a diagnosis of Eclampsia. Eclampsia was defined according to the working protocol as development of generalized fits in a woman with a blood pressure of 140/90 mmHg or higher and proteinuria of + or higher on dipstick without any recognizable cause. Referents were normotensive women who sought maternity services (*i.e.* including mothers cared in labor ward or due to other obstetric reasons including routine antenatal clinic attendance) at MNH around the time of admission of a case to ICU.

All consecutive admissions to ICU with a diagnosis of eclampsia and who met the criteria were prospectively enrolled as cases until the desirable sample size was realized. For every enrolled eclamptic woman, one referent woman who best matched the case in terms of age, parity, gestation age, status and mode of delivery was identified. The matching variables corresponded to the status of the case at the onset of the fit. For example, if the fit occurred before labor, the match was a normotensive pregnant woman who is not in labor among mother who were seeking maternity services at around the time of admission of the patient and who made the best match with the rest of matching variables (*i.e.*, age, parity, gestation age). Mothers were excluded from the study if they were of unsound mind, had developed eclampsia more than 72 hours after delivery, or could not communicate verbally.

In sample size estimation, we wished to compare the incidence of visual disturbance among eclamptic women with the referent women. The incidence of visual disturbance was taken as 32% for eclamptics. We hypothesized that the incidence among referent group of women would

be lower, say 15%. Thus the calculated minimum required sample size would be 216, that is, 108 eclampsia and 108 referent women assuming 95% confidence and power of 80% [32].

2.3. Data Collection

Data were collected using interviewer administered semi structured and checklist questionnaires. Information was obtained both directly from the women and from the case notes. Women who had experienced eclamptic fits were asked their experiences with the occurrence and characteristics of headache, visual disturbances, abdominal pain, nausea and vomiting preceding their fit(s).

2.4. Data Analysis

Data were coded and entered into computer using Epi data program. The software used for analysis was IBM SPSS statistics 19. Comparison of proportions used x^2 and Fischer exact test. Continuous or ordinal data were compared using a t-test with the assumption of equal variance.

In the analysis, the location of headache was described according to standard anatomical divisions of the head and its severity using a four grade scale (4GS). According to the 4GS pain severity was scored as; no pain (0), mild (1), moderate (3) and severe pain (4). The 4GS has been found to be as effective as the visual analogue scale (VAS) by other researchers [33]. Visual symptoms were characterized as blurring, blind sports, photophobia, and total blindness consistent with other studies [34-36]. Other symptoms include abdominal pain (type and location) and nausea/vomiting.

3. RESULTS

During the study period 130 eclamptic women were admitted, of which 7 did not fulfill the inclusion criteria. Thus, 123 were enrolled for the study as cases and were matched with 123 normotensive women (referents) to make up a total of 246 women for the study. For eclamptic women, age ranged from 16 to 37 years with a median of 22 years. The mean gestation age was 35.5 weeks and the mean parity was 2. A total of, 83 (68%) eclamptic women had delivered and 40 (32%) had not delivered at the time of interview **(Table 1)**.

Majority of eclamptic women (70%) were between 20 - 35 years of age. Most of them were primipara (68%), about half of them were at term.

As seen from **Table 2**, generally a significantly bigger proportion of eclamptic women presented with morbid symptoms (90%) compared with normotensive mothers (54%). Headache and visual problems in particular were significantly more frequent in eclamptics than in referent

Table 1. Characteristics of eclamptic and normotensive women. Data presented as n (%).

Characteristic	Eclamptic	Normotensive	Total
Age (yrs)			
<20	36 (29.0)	35 (29.0)	71 (29.0)
20 - 35	86 (70.0)	86 (70.0)	172 (70.0)
>35	1 (1.00)	2 (1.00)	3 (1.00)
Parity			
Primigravida	82 (67.0)	85 (69.0)	167 (68.0)
Multipara	41 (33.0)	38 (31.0)	79 (32.0)
Gestation Age (weeks)			
<28	3 (2.40)	1 (1.00)	4 (2.00)
28 - 37	52 (42.3)	54 (44.0)	106 (43.0)
≥37	68 (55.3)	68 (53.0)	136 (55.0)
Delivery			
Delivered	83 (68.0)	86 (70.0)	169 (69.0)
Undelivered	40 (32.0)	37 (30.0)	77 (31.0)

Table 2. The proportion of women presenting with symptoms of or similar to imminent eclampsia during the index pregnancy. Data presented as n (%).

Characteristic	Eclamptics n = 123	Normotensive n = 123	p value
Headache			
Yes	108 (88.0)	53 (43.0)	<0.001
No	15 (12.0)	70 (57.0)	
Visual problem			
Yes	48 (39.0)	4 (3.00)	<0.001
No	75 (61.0)	119 (97.0)	
Abdominal pain			
Yes	58 (47.0)	47 (38.0)	0.156
No	65 (53.0)	76 (62.0)	
Nausea			
Yes	74 (60.0)	66 (54.0)	0.303
No	49 (40.0)	57 (46.0)	
Vomiting			
Yes	76 (62.0)	71 (58.0)	0.516
No	47 (38.0)	52 (42.0)	
One or more symptom[a]			
Yes	111 (90.0)	66 (54.0)	<0.001
No	12 (10.0)	57 (46.0)	

[a]Headache, visual problems, abdominal pain and nausea/vomiting.

group [(88% vs 43%) and (39% vs 3%) respectively].

Eclamptic headache was characteristically more severe among cases with a mean score of 2.07 (±0.99 SD) compared with 0.65 (±0.85 SD), (95% CI: 1.18 - 1.65) for referents. As can be seen in **Table 3**, 46.3% of the cases reported severe headache compared to 5.7% of the referent group. The location of headache among eclamptic women was mainly frontal (65.7%) in contrast to frontal (41.5%) or generalized locations (39.6%) for the referent women.

Table 3. Characteristics of symptoms as experienced by eclamptic and normotensive women during the index pregnancy. Data presented as n (%).

Characteristic	Eclamptics n = 108	Normotensive n = 53	p value
Headache severity			
Mild	12 (11.1)	29 (54.7)	
Moderate	46 (42.6)	21 (39.6)	<0.001
Severe	50 (46.3)	3 (5.70)	
Site of headache			
Frontal	71 (65.7)	22 (41.5)	
Occipital	4 (3.70)	1 (1.90)	
Parietal	11 (10.2)	7 (13.2)	0.01
Vertex	5 (4.60)	2 (3.80)	
Generalized	17 (15.7)	21 (39.6)	
Site of abdominal pain			
Upper	21 (36.2)	4 (8.50)	
Lower	32 (55.2)	26 (55.3)	<0.001
General	5 (8.60)	17 (36.2)	
Type of pain			
Dull aching	12 (20.7)	5 (10.6)	
Colicky	21 (36.2)	17 (36.2)	
Cramping	8 (13.8)	16 (34.0)	<0.321
Burning	7 (12.1)	2 (4.30)	
Other	10 (17.2)	7 (14.9)	
Severity of nausea			
Non severe	44 (60.0)	45 (68.0)	
Severe	20 (27.0)	15 (23.0)	0.529
Very severe	10 (13.0)	6 (9.00)	
Type of vomiting			
Projectile	4 (5.00)	0 (0.00)	0.121
Non projectile	72 (95.0)	71 (100.0)	

Very few (3%) normotensive women reported visual problems **(Table 3)**. Regarding eclamptic women who presented with visual problems, the complaints were blurring of vision (94%), blind spots (67%), photophobia (21%) and total blindness (15%).

Although abdominal pain was commonly reported by both the cases and referent women, upper right quadrant abdominal pain was significantly more reported by eclamptic women(36.2%) than the normotensive (8.5%), p = 0.001. Nausea and vomiting were not significantly different in occurrence, severity and character among the two groups.

Among eclamptic women who presented with headache (89%) or abdominal pain (71%), fits occurred within 7 days of the symptom. Almost all mothers (98%) who reported visual problems had fits within 12hours. Most cases of nausea (63%) and vomiting (62%) preceded eclamptic fits by more than 7 days **(Table 4)**.

4. DISCUSSION

Eclampsia continues to lead as a cause of maternal deaths despite the availability of effective prophylactic treatment. The clinical challenge lies in predicting which women with a diagnosis of pre-eclampsia will soon progress into eclampsia. Headache, visual disturbances, abdominal pain, nausea, and vomiting are the most consistent prodromal symptoms of eclampsia. These symptoms have the potential to alert health service providers on

Table 4. Time elapse from onset of symptoms to development of fits among eclamptic women.

Characteristic	Number	Percent
Headache (n = 108)		
0 - 7 days	96	89.0
>7 days	12	11.0
Abdominal pain (n = 58)		
0 - 7 days	41	71.0
>7 days	17	29.0
Nausea (n = 74)		
0 - 7 days	27	37.0
>7 days	47	63.0
Vomiting(n = 76)		
0 - 7 days	29	38.0
>7 days	47	62.0
Visual problems (n = 48)		
0 - 12 hours	47	98.0
>12 hours	1	2.00

which patient is most likely to benefit from prophylactic treatment for eclampsia while minimizing potentially harmful interventions and cost [24,25]. Although the ability of these symptoms to predict adverse maternal outcomes is supported by some researchers [21,25] it has been questioned by others [27]. Moreover, similar symptoms are common among normal pregnant mothers and can be confused with symptoms caused by tropical infections such as malaria [8,28-31]. With this background it was imperative to attempt to characterize the prodromal symptoms and distinguish them from similar symptoms usually experienced by normotensive women in pregnancy.

We found that prodromal symptoms occurred in 90% of eclamptic women which is within the 41% to 91% range commonly reported in literature [24,25,37,38]. In the current study, among the prodromal symptoms, headache was the most experienced (88%) by eclamptic women which is comparable with the 81% incidence in a recent study of eclamptic women in Nothern Tanzania [24]. In addition, our study proves that headache is significantly commoner among eclamptic than non eclamptic pregnant women.

Headache and visual disturbance are recognized neurological manifestations of severe pre-eclampsia that share a common pathophysiological base [22,26,31]. It was therefore not surprising to note that visual disturbance was the second most frequent prodromal symptom in the current study-a pattern which has been reported by others [24,34,39]. Among eclamptic women headache was characteristically frontal and severe with the first eclamptic fit occurring within one week of its onset in contrast to headache among the normotensive women in whom it was frontal or generalized and mild in severity. There are few studies that have described prodromal symptoms of eclampsia. Katz and colleagues in USA noted that eclamptic mothers described headache as "the worst headache of their lives" [26,31]. Frontal headache in relation with eclampsia has also been reported by some [18], but not supported by others who variably describe it as bitemporal, occipital, diffuse or only occasionally frontal [26,31]. It is unclear whether the difference is a true variation among study populations or it is due to study biases. Further studies are needed to clarify this difference.

Visual problems were reported by two fifth of all eclamptic women with blurring of vision being the most common presentation, followed by blind spots, photophobia and total blindness. Although the incidence of visual problems ranked second to headache, it is the most ominous symptom as in almost all eclamptic women fits occurred within 12hours of its onset. This is probably because the changes like brain oedema, microvascular thrombosis and necrosis that cause visual symptoms would almost immediately lead to epileptic fits [22]. In support to this notion, visual problems were rarely reported in normotensive mothers with only 4 women presented with visual complaints.

The presentation with upper right quadrant abdominal pain, was statistically significantly higher in eclamptics than normotensive mothers probably due to its linkage with liver pathophysiological changes in severe pre-eclampsia. Upper abdominal pain, as is the case with nausea and vomiting, are all linked with liver injury [17, 21,25,26] but the importance of these symptoms in predicting eclampsia has been unsatisfactory due to low sensitivity. Other types of abdominal pain, nausea and vomiting were largely indistinguishable from similar symptom experiences by normotensive mothers. This implies that the symptoms represent a more heterogeneous group caused by a variety of factors.

The interpretation of our findings is limited in that the patients' account on prodromal symptoms was retrospective hence subject to recall bias. However, a short duration for the symptoms (during index pregnancy) and the design to interview the mothers immediately after an eclamptic fit should have minimized such a bias. Our decision to interview eclamptic mothers rather than reliance on the case note records is one of the strengths of this study in contrast to similar studies that have used retrospective data [21,25-26]. The characteristics of the prodromal symptoms established by this study could be used to develop a prediction model for eclampsia in the process to improve management of pre-eclamptic patients and prevention of eclampsia.

In conclusion, headache, abdominal pain, nausea and vomiting are common during pregnancy whether or not complicated by eclampsia but visual disturbances were not as common in normotensive mothers. The characteristics of headache and visual disturbances can be reasonably distinguished among eclamptics and normotensive women. Visual disturbance is the most ominous for occurrence of eclamptic fit within twelve hours. General abdominal pain, nausea and vomiting are heterogeneous and not distinguishable among eclamptic and normotensive women.

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