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Relationship of Age of Onset of Epilepsy to History of Febrile Seizures and Neurocognitive Deficit Among Hausas of Northern Nigeria

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ABSTRACT

Fever is characterized by increase in the temperature of nervous tissues which could enhance the rate, or magnitude of neuronal firing, leading to seizures. This study was designed to investigate the relationship between the age of onset of seizure with gender, history of febrile seizure and neurocognitive deficit among the Hausas of Northern Nigeria. It was a prospective study involving 105 epilepsy patients (61 males and 44 females) of a wide age spectrum. A Pearson's Chi square was used to establish a relationship between the variables of interest. The data was analyzed using SPSS version 20 with $p < 0.05$ as level of significance. The result showed that there was no gender difference in the age of onset of seizure in the study group. A relationship was observed between age of onset of seizure with history of febrile seizure (χ^2= 18.01, $p < 0.001$) and neuronal deficit (χ^2= 12.93, P= 0.002). A significant relationship was also noticed between neuronal deficit and febrile seizure (χ^2= 4.02, p = 0.045). In conclusion, age of onset of febrile seizure may be one of the markers to be used in ruling out some of the epilepsy associated disorders or problems.

Keywords: Age, epilepsy, fever, neurocognitive deficit, Hausas.

INTRODUCTION

Fever is characterized by increase in the temperature of nervous tissue which could enhance the rate, or magnitude of neuronal firing, leading to seizures (Dubé et al. 2007). Fever-provoked seizure is termed febrile seizure while epilepsy is a chronic disorder of the central nervous system characterized by recurrent seizures (Mastrangelo et al. 2005). Epilepsy is the commonest neurological condition affecting up to 70 million people worldwide (Ngugi et al. 2010). Developing countries such as Latin America and several African countries, notably Liberia, Nigeria and United Republic of Tanzania record a higher prevalence when compared with the prevalence rates of between 4 to 6 per 1000 documented in the United States (Hauser et al. 1991; Senanayake and Roman 1993). In Nigeria, the prevalence of epilepsy varies from 15 to 37 per 1000 (Reynolds 1988). However one of the early publications on the prevalence of epilepsy in Nigeria reported a prevalence of between 8 and 13 per 1000 in the urban communities of Lagos, 5.3 per 1000, and 6.2 per 1000 among the inhabitants of Udo and Igbo-ora, respectively. The variation in the prevalence rate may probably be due to differences in health facilities between the different communities (Dada 1970; Longe and Osuntokun 1989; Osuntokun et al. 1987; Olubunmi 2006). The high and fluctuating prevalence of epilepsy necessitates the search for risk factors associated with its onset.

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A study by Ogunniyi of 155 Nigerian epileptic patients concluded that febrile convulsions and head trauma were significant risk factors for epilepsy (Ogunniyi et al. 1987). However, other authors confirmed the importance of birth asphyxia, intracranial infections, hereditary factors and head injuries as important risk factors (Osuntokun 1978; Danesi 1985). Family history of febrile seizures, perinatal factors, temperature peak, maternal smoking and alcohol consumption during pregnancy are also additional factors, but several risk factors remain largely unknown (Johnston 2004; Kalra 2004). Retrospective studies from epilepsy centres have documented that history of prolonged febrile seizures in childhood is associated with development of intractable temporal lobe epilepsy in many adults. However, population based studies have failed to ascertain this relationship (Baram and Shinnar 2002; Shinnar and Glauser 2002).

The age distribution of epilepsy in Nigerians appears similar to that described among the Caucasians (Olubunmi 2006). Among adult Nigerians, a study reported a mean age of 21 years with predominance of partial seizures (Ogunniyi et al. 1998). Other investigators confirmed this preponderance of partial seizures among children over 5 years of age (Obembe and Ahmed, 1988). It was also reported that the onset in 68% of patients were in the first and second decades of life (Osuntokun et al. 1974). In communities with comprehensive health facilities, the highest age-specific prevalence ratio occurring below the age of 20 years was within the 5 to 14 years age group (Olubunmi, 2006). It was also noted that early epilepsy onset was consistent with particular biological features in the maturing brain that contribute to its hyper excitability (Velı´skova´ et al. 2004). There is a growing list of indications in the literature that epilepsy patients with history of febrile seizures seem to have a more serious condition than those without, as they demonstrated a higher seizure frequency of both partial and generalized seizures (Heuser et al. 2011).

Significantly, several previous studies have indicated that temporal lobe epilepsy and febrile seizures may have a common genetic basis (Baulac et al. 2001; Schulz and Ebner 2001). On the other hand it is still one of the controversial topics whether febrile seizures are related to temporal lobe epilepsy with some authors confirming such a link and others showing the opposite (Annegers et al. 1987; Cendes et al. 1993; Kuks et al. 1993; Berg et al. 1999; Bower et al. 2000). This may indicate population specific association of febrile seizures and onset of epilepsy. This would also indicate the need for ethnicity wise investigation of this relationship. An important issue that remains unresolved is whether hippocampal neuron loss precedes the seizure onset or is a result of repeated seizures, especially prolonged seizures.

This study was aimed at determining the relationship between the age of onset of seizure with gender, history of febrile seizures and neurocognitive deficit with the objectives of determining the role of gender in the onset of epilepsy, the age range at which the child with history of febrile seizures is likely to have an onset of epilepsy and the risk associated with febrile seizures.

MATERIALS AND METHODS

The study was conducted in the North-western Nigerian city of Kano with majority of the population belonging to the Hausa ethnic group. The study participants were recruited from the Kumbotso Epilepsy Clinic and the Aminu Kano Teaching Hospital (AKTH).

105 epilepsy patients (61 males and 44 females) were involved in the study. Ethical clearance was obtained from the research ethical committee of the AKTH. An informed consent was sought from the participants and/or parents or guardians. Only patients who belong to the Hausa ethnic group were included in the study. The data were collected prospectively using a questionnaire that was designed to collect basic sociodemographic data such as sex, age and ethnicity as well as clinical data such as age of onset of epilepsy, history of febrile seizures, etc. Neurocognitive deficit was assessed using bedside general neurological examination in which the sensorium, the cranial nerves, the motor system, the sensory system and cerebellar functions were examined. Cognitive deficit was examined by beside assessment of higher cortical functions such as attention and concentration, orientation, memory, speech, object recognition and naming, speech comprehension and, praxis. The bedside cognitive testing took due regard of the patients' respective age.

The data was presented using simple frequency to indicate prevalence. The level of relationship was determined using Pearson's chi square/ Fisher's exact tests. All analyses were carried out using SPSS version 20 statistical software and differences between the groups were considered statistically significant at $P \leq 0.05$ with +/- 1.96 as a critical value for the post hoc test.

RESULTS

Table 1 shows no statistically significant relationship ($\chi^2 = 0.458$, $P = 0.791$) between age of onset of epileptic seizure and gender. The most frequent of age of onset was above 15 years of age and least at less than five years of age in both sexes. In males 5 – 15 years age group, the highest frequency was observed whereas in females the highest frequency was observed in the > 15 years age group.

Table 2 shows a statistically significant relationship ($\chi^2 = 18.01$, $P < 0.001$) between age of onset of epilepsy and history of febrile seizures. The subjects

Table 1: Relationship between sex and age of onset of epileptic seizures

Variable			Sex		Total
			Male	Female	
Age of onset of epilepsy	< 5 years	Count	18	12	30
		Expected Count	17.4	12.6	30.0
		Residual	0.6	-0.6	
		Standard Residual	0.1	-0.2	
	5- 15 years	Count	22	14	36
		Expected Count	20.9	15.1	36.0
		Residual	1.1	-1.1	
		Standard Residual	0.2	-0.3	
	> 15 years	Count	21	18	39
		Expected Count	22.7	16.3	39.0
		Residual	-1.7	1.7	
		Standard Residual	-0.3	0.4	
Total		Count	61	44	105
		Expected Count	61.0	44.0	105.0

$\chi^2 = 0.47$, P = 0.79

Table 2: Relationship between age of onset of epilepsy and febrile seizures

Variable			History of febrile seizure		Total
			Yes	No	
Age of onset of epilepsy	< 5 years	Count	22	5	27
		Expected Count	13.5	13.5	27.0
		Residual	8.5	-8.5	
		Standard Residual	2.3	-2.3	
	5- 15 years	Count	13	16	29
		Expected Count	14.5	14.5	29.0
		Residual	-1.5	1.5	
		Standard Residual	-0.4	0.4	
	> 15 years	Count	7	21	28
		Expected Count	14.0	14.0	28.0
		Residual	-7.0	7.0	
		Standard Residual	-1.9	1.9	
Total		Count	42	42	84
		Expected Count	42.0	42.0	84.0

$\chi^2 = 18.46$, P< 0.001

with history of febrile seizures showed higher frequency at younger ages (< 5 years) and least frequency at older ages (> 15 years). The opposite trend was observed in subjects with no history of febrile seizures.

A statistically significant relationship (χ^2= 12.93, P = 0.002) was observed between the age of onset of epilepsy and neurocognitive deficits. The neurocognitive deficits were higher in subjects with earlier age of onset (< 5 years) and least in those with later age of onset (> 5 years) (Table 3).

Table 4 shows relationship between neurocognitive deficits and history of febrile seizures showing a statistically significant association (χ^2= 4.02, P = 0.045). A lower frequency was observed in the subjects with both neurocognitive deficits and febrile seizures compared to those with absence of these traits.

DISCUSSION

In this study, the male patients showed higher frequency in all the age of onsets. However, there was no significant association between the ages of onset of epileptic seizure with gender. This indicates gender insensitivity in the onset of the epilepsy.

The higher frequency seen in the male subjects may be linked to other etiological factors such as head trauma which is known to be commoner in males (Ogunniyi et al. 1987). In addition, the male to female ratio with respect to etiology was found to be in favor of male as reported in several other studies (Preux and Druet-Cabanac 2005; Olubunmi 2006). Other African studies have reported a slight male predominance (Osuntokun 1987). It was documented that, in most parts of Africa, males more readily attend the health care centers for socioeconomic reasons, making them to be over represented on hospital based studies (Olubunmi 2006).

The relationship between age of onset of epilepsy and history of febrile seizures among Hausas was evaluated. The subjects with history of febrile seizures show higher frequency at early ages (< 5 years) and least frequency at older ages (> 15 years). The opposite trend was observed in subjects with no history of febrile seizure. Moreover, in the present study it was noted that the association was stronger in the first and second halves of the first and second decades of life, respectively. The probable reason for such is that postnatal brain development is more elaborate before age of seven, due to the ability of the cranial expansion to

Table 3: Relationship between age of onset of epilepsy and neurocognitive deficits

Variable			Neurocognitive deficit		Total
			Yes	No	
Age of onset of epilepsy	< 5 years	Count	7	22	29
		Expected Count	2.5	26.5	29.0
		Residual	4.5	-4.5	
		Standard Residual	2.8	-0.9	
	5- 15 years	Count	2	34	36
		Expected Count	3.1	32.9	36.0
		Residual	-1.1	1.1	
		Standard Residual	-0.6	0.2	
	> 15 years	Count	0	39	39
		Expected Count	3.4	35.6	39.0
		Residual	-3.4	3.4	
		Standard Residual	-1.8	0.6	
Total		Count	9	95	104
		Expected Count	9.0	95.0	104.0

Fisher's Exact Value = 11.30, P= 0.001

Table 4: Relationship between neurocognitive deficits and febrile seizures

Variable			History of febrile		Total
			Yes	No	
Neurocognitive deficit	Yes	Count	6	1	7
		Expected Count	3.5	3.5	7.0
		Residual	2.5	-2.5	
		Standard Residual	1.4	-1.4	
	No	Count	36	42	78
		Expected Count	38.5	39.5	78.0
		Residual	-2.5	2.5	
		Standard Residual	-0.4	0.4	
Total		Count	42	43	85
		Expected Count	42.0	43.0	85.0

Fisher's Exact Test , P = 0.05

accommodate such activity (Dekaban 1978; Stiles 2008). For the second decade, the hormonal contribution (testosterone and estradiol) may dominate any other factors (Sisk and Zehr 2005; Stein 2008; McCarthy 2009).

A statistically significant relationship was observed between the age of onset of epilepsy and neurocognitive deficits. The neurocognitive deficits were higher in subjects with early age of onset (< 5 years). It was generally noted that epilepsy affects the intellectual abilities of people with epilepsy, which may have a negative effect on their overall school performance (Ibekwe et al. 2007; Sunmonu et al. 2008). It has been reported that factors associated with poor intelligence include early age of onset of seizure as well as other factors that include, seizure type, seizure frequency and long duration of epilepsy (Ibekwe et al. 2007; Sunmonu et al. 2008). The present study support these earlier finding related to the fact that the immature brain is more prone to develop seizures and that it might be resistant to seizure induced damage compared to the adult brain (Haut et al. 2004). Other studies have suggested that kindled seizures induce progressive cellular and metabolic alterations correlated with neuronal loss in the hippocampus, neurogenesis, increased susceptibility to evoked and spontaneous seizures, and behavioral and cognitive deficits that worsen as a function of the cumulative number of seizures (Pitkanen and Sutula 2002; Lukoyanov et al. 2004). Epilepsy patients are at significant risk for cognitive impairment and behavioral abnormalities (Elger et al. 2004). Specifically, temporal lobe epilepsy is associated with memory deficits (Kim et al. 2003).

It is noteworthy that the influence of frequency of seizures, seizure onset, and duration of epilepsy on memory of children with temporal lobe epilepsy is poorly understood (Bigel and Smith 2001). Previous authors have also found association between memory deficits and temporal lobe epilepsy among children (Hershey et al. 1998; Bigel and Smith 2001). It was reported that patients who presented with deficits in story memory recognition had lower age of seizure onset, suggesting that earlier onset of epilepsy may be related to the damage of verbal storage processes. Hence, supporting the view of hippocampal atrophy which usually extends beyond to include; amygdala, entorhinal cortex and parahippocampal gyrus among the patients (Du et al. 1993; Guimarães et al. 2014). It may therefore be seen that the neurocognitive deficits in epilepsy may involve much of the areas involved in memory and verbal processing.

The present study also reported the relationship between neurocognitive deficits and history of

febrile seizures in this study. A lower frequency of what was observed in the subjects with both neurocognitive deficits and febrile seizures compared to those with absence of both traits. This relationship may serve as additional support for the association between age of onset of epilepsy and neurocognitive deficit. There is evidence to suggest that hippocampal neuron loss is a progressive process that accompanies the development of seizures (Mathern et al. 1995). It was noted that in patients with temporal lobe epilepsy (associated with hippocampal sclerosis), the early age at onset of the seizures, a history of complex febrile seizures and other early insults, increased the incidence of seizures among family members. Memory deficit and hippocampal atrophy on MRI are features that distinguish this entity from other causes of mesial temporal lobe epilepsy (Williamson et al. 1985).

CONCLUSIONS

In conclusion, the age of onset of febrile seizure is not gender specific. The child who experienced a febrile seizure may likely encounter an onset of epilepsy in < 5 and after 15 years of age. The child with earlier onset of seizure (< 5 years) may likely experience neurocognitive deficit. There may be a contribution of febrile seizures to the manifestation of neurocognitive deficit.

Limitations

As inherent with every research, the current research is associated with some limitations. The duration of febrile seizure was not known. The assessment of patients was purely clinical and not supported by investigative tools such as EEG and neuroimaging. Other important risk factors such as intracranial infections, head injuries that may cause seizures were impossible to exclude.

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Conflict of interest

None declared

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