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Maternal and fetal outcome in women with epilepsy associated with neurocysticercosis

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ABSTRACT – *Aim.* We wanted to characterize the clinical profile and outcome of pregnancy in women with epilepsy due to neurocysticercosis (NCC) enrolled in the Indian Registry of Epilepsy and Pregnancy (IREP).*Methods.* We identified all women with NCC in the IREP between January 2000 and September 2005. Age- and parity-matched patients without NCC were identified from the respective centers of IREP for comparison. Statistical analysis was performed using SPSS version 11.

Results. There were 30 women with NCC (mean age 24.3 ± 4 years) among 1071 registrations in the IREP. All the patients had NCC prior to the pregnancy. Fourteen (47%) NCC patients had calcified lesions and 16 (53%) had ring lesions in a CT scan of the brain. Compared to women without NCC, the NCC group had later age-at-onset of seizures (20.7 ± 4.4 years, p = 0.008) and epilepsy (21.1 ± 5.2 years, p = 0.01). They were more likely to have partial seizures (70% *versus* 30%, p = 0.002), an EEG without epileptiform abnormalities (50% *versus* 100%, p = 0.01), and better control of seizures before (47% *versus* 3%, p = 0.001) and during pregnancy (33% *versus* 10%, p = 0.02). Maternal and neonatal complications did not differ between the groups.

Conclusions. NCC is an uncommon cause of epilepsy in pregnant women enrolled in IREP. To be noted, as a limitation of our study, that the IREP is a hospital-based registry, which may not reflect global epilepsy characteristics of the community. The maternal and fetal outcome for NCC patients was not different from those women without NCC.

Key words: neurocysticercosis, epilepsy, pregnancy registry, India, IREP

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Neurocysticercosis (NCC) is a major public health problem in India, Latin American, and south East Asian countries (Rajshekhar *et al.* 2003b). NCC has become an important emerging infection in the industrialized world

due to increased travel and immigration of people from endemic areas (Wallin and Kurtzke 2004). In a recent community survey, it accounted for 34% of patients with active epilepsy and 50% of patients presenting with partial seizures in hospital-based studies (Garg *et al.* 2000, Rajshekhar *et al.* 2003a, Rajshekhar *et al.* 2006). Single enhancing CT-documented lesions (SECTL) account for 30-50% of hospital patients with partial seizures in certain geographical areas in India (Garg *et al.* 2000, Rajshekhar *et al.* 2003a, Rajshekhar *et al.* 2006).

Parenchymal cysticercosis, the most frequent form of NCC, presents with acute symptomatic seizures. About 50% of these patients will experience a seizure recurrence within 7 years of the first symptoms. Almost half of these recurrences will occur in the first year (Carpio and Hauser 2002). The high seizure recurrence after a first acute symptomatic seizure is related to the persistence of active CT brain lesions (Carpio and Hauser 2002). Nearly 85% of patients with a SECTL have good seizure outcome following resolution of the lesion. However, recurrence of seizures can be expected in about 15% of patients (Rajshekhar and Jeyaseelan 2004). Patients with more than two seizures, those with breakthrough seizures, and those whose follow-up CT shows a calcified residue of the granuloma, have a higher risk of recurrence (Rajshekhar and Jeyaseelan 2004). Patients with NCC who develop perilesional gliosis develop intermittent symptoms such as sensations of heaviness or weightlessness, dystonic posturing, numbness and alien hand phenomenon on the side contralateral to the cerebral lesion (Pradhan *et al.* 2003).

The high seizure recurrence rates observed in NCC patients make them a high-risk group for seizure recurrence during pregnancy. Seizures occurring in NCC patients during pregnancy could be harmful to the mother and the fetus. The seizure, maternal and fetal outcome in women with NCC is largely unknown.

Our aim was to characterize the clinical profile and outcome of pregnancy in women with epilepsy due to NCC. We hypothesized that seizure, fetal and maternal outcome would be different in pregnant women with NCC.

Materials and methods

This study was carried out as a part of the Indian Registry for Epilepsy and Pregnancy (IREP) program. The IREP was started in 2000 with three centers [*Sree Chitra Tirunal Institute for Medical Sciences and Technology* (SCTIMST), *Thiruvananthapuram, Andhra Medical College* (AMC), *Visakhapatnam and Christian Medical College* (CMC), *Ludhiana*]. The IREP is a multidisciplinary, hospital-based registry. Patients are referred by physicians and obstetricians to the appropriate centers. Women with epilepsy (WWE) are enrolled in the IREP in the pre-pregnancy or early pregnancy period (before fetal outcome is known), and are followed up prospectively according to a standard protocol (Thomas *et al.* 1999, Thomas *et al.* 2001). Clinical and laboratory investigations were carried out at predetermined intervals as laid down in the protocol. Each patient maintained a daily diary for drug compliance (antiepileptic drugs and folic acid) and seizure count, which was scrutinized by the investigator while updating the monthly records of that patient in the IREP. Good compliance was considered as patients taking medicines without any default, or, where there had been one or two exceptions to compliance, or, there had been no breakthrough seizures.

Terminology according to the International League Against Epilepsy (ILAE) was followed in classifying seizures (ILAE 1981) and epileptic syndromes (ILAE 1989). The diagnosis of NCC (definitive or probable NCC, based on the absolute, major, minor and epidemiological criteria) or SECTL (seizures without raised intracranial pressure or focal deficits, and absence of systemic illness; a solitary enhancing lesion on CT of ≤ 2 centimeters without midline shift), was made according to the published criteria (Del Brutto *et al.* 2001, Rajshekhar and Chandy 1997).

The next adjacent woman without NCC enrolled in the respective center of the IREP, matched for age and parity (for each case of NCC) was selected as the comparison subject. Demographic data such as age, education, occupation and family income were documented. The seizure and epilepsy characteristics (age-at-onset of seizure, epilepsy, seizure types, frequency of seizures in the preconception phase, during the pregnancy and postnatal period) and antiepileptic drug (AED) details and folic acid usage were collected for both NCC patients and the comparative group. Seizure frequency was documented as daily, weekly, monthly, infrequent and no seizures. Seizure outcome was classified as (good-infrequent and no seizures *versus* poor-frequent seizures on daily, weekly, monthly basis). Maternal complications during pregnancy, type of delivery, and birth weight of the baby were recorded. Major congenital malformations were ascertained in the infant by clinical examination, echocardiography and abdominal ultrasonography in all cases and controls. The IREP was approved by the hospital research committees in each center.

Statistical analyses were performed using SPSS version 11. Fisher's exact test was used to compare the different variables between the NCC and the comparative groups. The means of the continuous variables were compared between the two groups using Student's t-test. A $p < 0.05$ was considered significant.

Results

There were 30 women (SCTIMST 4/738, AMC 11/250 and CMC 15/83, mean age 24.3±4) with NCC among the 1071 registrations in the IREP between 2000 and 2005. NCC was diagnosed before pregnancy in all patients. Five

(17%) patients fulfilled the definitive criteria for NCC (cystic lesions showing the scolex on CT), and the other 25 (83%) patients had probable NCC (lesions highly suggestive of NCC on neuroimaging studies, clinical manifestations suggestive of NCC and individuals living in an endemic area or traveling to an endemic area).

Seizure and epilepsy characteristics

The NCC group had a later age-at- onset of the first seizure and epilepsy (*table 1*). The mean duration of the epilepsy in women in the NCC group was shorter than the compartive group (*table 1*). They had predominantly partial seizures and a localization-related epilepsy syndrome. In the comparative group, there were 17 (57%) patients with a generalized epilepsy syndrome (seven with juvenile myoclonic epilepsy, 10 with idiopathic). Thirteen patients (43%) had a localization-related epilepsy syndrome with secondarly generalized seizures (two symptomatic, 11 cryptogenic). EEG was performed in 21 (70%) NCC patients and it was abnormal in six (29%) (focal spikes in three, and focal slowing in three). The NCC group was more likely to have an EEG without epileptiform abnormalities (*table 1*). The NCC group had good seizure control both before and during pregnancy (*table 2*).

Table 1. Demographic, seizure and epilepsy characteristics between the NCC and the comparative groups.

Characteristic	NCC (n = 30)	Comparative group (n = 30)	p values
Age mean (years) ± SD[a]	24.3±4	25.8±4.3	0.17
			1.0
Family income / month			
Less than Rs. 10,000[b]	19 (63%)	19 (63%)	
More than Rs. 10,000	11 (37%)	11 (37%)	
Age of onset of seizure (years) ± SD	20.7 ± 4.4	16.8±6.1	0.008
Age of onset of epilepsy (years) ± SD	21.1 ± 5.2	17.7±5.6	0.01
Duration of epilepsy (months) ± SD	44.9 ± 54	93.9±87	0.01
			0.004
Seizure classification			
Partial seizures	21 (70%)	9 (30%)	
Generalized seizures	9 (30%)	21 (70%)	
			0.001
Epileptic Syndrome			
Localization related epileptic syndrome	20 (67%)	13 (43%)	
Generalized epileptic syndrome	10 (33%)	17 (57%)	
Anti-epileptic drugs used[b]			
Nil	2 (7%)	1 (3%)	1.0
Phenobarbitone	2 (7%)	3 (10%)	1.0
Carbamazepine	14 (47%)	11 (37%)	0.60
Phenytoin[c]	10 (33%)	3 (10%)	0.05
Sodium Valproate	3 (10%)	8 (27%)	0.18
Others	6 (20%)	7 (23%)	1.0
			NA[d]
CT Scan			
Normal	-	23 (100%)	
Abnormal	30 (100%)	-	
			0.004
MRI Scan			
Normal	0 (0%)	4 (67%)	
Abnormal	13 (100%)	2 (33%)	
			0.03
EEG			
Presence of spike discharges	3 (50%)	10 (100%)	
Presence of focal slowing	3 (50%)	0 (0%)	

[a] SD – standard deviation.
[b] Rs – Indian Rupees, Rs 10000 is equivalent to US$ 216.
[c] The proportion of patients on Phenytoin was different from the comparative group even though Carbamazepine was frequently used in NCC group.
[d] NA – not applicable.

Table 2. Seizure, maternal and fetal outcomes between the NCC and the comparative groups.

	NCC (n = 30)	Comparative group (n = 30)	P values
Seizure control before pregnancy			0.0002
Good[a]	14 (47%)	1 (3%)	
Poor	16 (53%)	29 (97%)	
Seizure control during pregnancy			0.05
Good	10 (33%)	3 (10%)	
Poor	20 (67%)	27 (90%)	
Maternal Complications			0.14
Yes	2 (7%)	7 (23%)	
No	28 (93%)	23 (77%)	
Neonatal complications			0.29
Yes	3 (10%)	7 (23%)	
No	27 (90%)	23 (77%)	
Congenital malformations			0.19
Yes	1 (3%)	5 (17%)	
No	29 (97%)	25 (83%)	
Major congenital malformation	0 (0%)	3 (10%)	0.49

Poor – frequent seizures [daily, weekly, monthly].
[a] Good – [no seizures and infrequent seizures].

AEDs and cysticidal drugs

Twenty (67%) NCC patients were on monotherapy, eight (26%) were on polytherapy and two (7%) patients were not on any AED. There was no significant difference in the AED preference between the two groups except for phenytoin, which was more commonly prescribed for the NCC group (33% *versus* 10%, p = 0.02) (*table 1*). AED compliance was good in both groups according to the drug and seizure dairy. Only six (20%) patients with NCC received albendazole therapy and none of these patients were treated with cysticidal drugs during pregnancy.

Neuroimaging findings

All of the imaging studies were performed before pregnancy. No imaging was repeated during pregnancy, even when seizure frequency had increased in some patients. CT scan abnormalities for the NCC group included ring-enhancing lesion (SECTL) in 16 (53%) and calcified lesion in 14 (47%) subjects. CT scan was performed in 23 (77%) patients in the comparative group and was normal in all of them. MRI results were available for 13 (43%) women with NCC and six (20%) subjects in the comparative group. The MRI was abnormal in all NCC patients and the findings were as follows; ring-enhancing lesions (peripheral enhancement with hypointense centre) eight (62%), disc lesion (uniform enhancement) four (31%) and calcification in one (7%) subject. Two (33%) of the six subjects in the comparative group had an abnormal MRI (porencephalic cyst in one and infarct in one, neither patients had a CT scan). The NCC group was more likely to have MRI abnormalities (*table 1*).

Pregnancy characteristics

Only two women with NCC were enrolled during the preconception phase in the IREP, which was similar to the comparative group (n = 2, p = 1.0). The mean duration of pregnancy at the time of enrolment in the NCC group was 4 ± 2 months, which did not differ from the comparative group (4.2 ± 2 months, p = 0.61). Only four NCC patients received folic acid during the preconception phase (controls – 6, p = 0.48).

Maternal and fetal outcome

In the NCC group, 16 (53%) women had full term, normal delivery, and in two (7%) subjects, forceps were used. Caesarian section was performed in 12 (40%) NCC patients and in 11 (37%) patients in the comparative group (p = 1.0). Maternal complications were seen in two women with NCC (one antepartum hemorrhage and one pre-eclampsia). Maternal complications did not differ between the two groups (*table 2*).
The mean birth weight of the infants born to women with NCC was 2.7 ± 0.52 kilograms, which was similar to the comparative group (2.8 ± 0.38 kilograms, p = 0.53). The mean head circumference of the infants in the NCC group was 34.5 ± 2.1 centimeters, which was different from the comparative group (33.3 ± 1.3 centimeters, p = 0.02).
Two babies were preterm and one baby was post-term in the NCC group. Complications occurred in three neonates

in the NCC group (two metabolic and one big baby). The neonatal complications did not differ between the two groups (*table 2*).

Malformations

There were no major malformations in the infants of women with NCC. A minor malformation was noted in one infant (hypertelorism) in the NCC group. In the comparison group, three infants had major malformations (one atrial septal defect, one hypospadiasis and one radial hypoplasia) and two had minor malformations (one with a flat nose, and one with digital hypoplasia). The frequency of congenital malformations did not differ between the two groups (*table 2*).

Discussion

We studied the clinical profile and outcome of pregnancy in women with epilepsy due to NCC. NCC was an uncommon (30/1071) cause of epilepsy in the women enrolled in our registry. Women with NCC had a different profile, with predominantly partial seizures, normal EEG and better seizure control, both before and during pregnancy. There were no differences in maternal and fetal outcome between NCC and the comparative groups.

The clinical profile of seizures and epilepsy in the NCC group was similar to other reported series (Cao *et al.* 1997, Chopra *et al.* 1992, Garg and Nag 1997, Rajshekhar 2003b, Singh *et al.* 2001). The mean age-at-onset of seizures and epilepsy was in the second decade among the NCC patients. In a previous report from India, 72% of NCC occurred in children and adolescents (Garg and Nag 1997). In another study, 78% of the NCC patients were between 11 and 20 years of age (Chopra *et al.* 1992). Neglect of personal hygiene, particularly among children and adolescents, could be making them more vulnerable to NCC (Cao *et al.* 1997).

Partial seizures were the commonest presentation in our NCC patients, which has also been observed in other series. Seventy percent of the patients had partial seizures in a report from India (Singh *et al.* 2001). Between 70–80% of patients, have partial seizures with or without secondary generalization (Rajshekhar 2003b). Generalized seizures and other forms of seizures also may occur in these patients (Rajshekhar 2003b). Only three (50%) patients with NCC had epileptiform abnormalities on EEG. In a large series of NCC, 76% of patients had normal EEG and only 5% of them had focal epileptiform abnormalities (Singh *et al.* 2001). The focal EEG abnormalities resolved after disappearance of the CT lesion (Sethi *et al.* 1994).

With regard to AED therapy, there was no significant AED preference; carbamazepine being the most commonly prescribed AED in the two groups. Nevertheless, phenytoin was more frequently used in the NCC group if it had been prescribed. Acute symptomatic seizure is the most common presentation in patients with NCC (Garg *et al.* 2000, Singh *et al.* 2001), and it is likely that these patients might have received intravenous phenytoin as the initial treatment to control seizures and thereafter might have been continued. This may explain the difference in phenytoin use between the two groups.

There are very few published data on the outcome of pregnancy in women with NCC. Worldwide there are only seven documented cases of NCC occurring during pregnancy (*table 3*). Five out seven patients had multiple cysts

Table 3. Clinical characteristics of patients with NCC during pregnancy reported in the literature (n = 7).[a]

Mean age (years)	25.1 (range 17 – 35)
Gestation weeks (mean)	16.8 (range 5 – 35)
Country	
USA	5
Mexico	1
United Kingdom	1
Symptoms	
Seizure	4
Headache	5
Papilledema	4
Blurred vision	2
Vomiting	4
Encephalopathy	2
Neuroimaging	
Multiple cysts	5
Intraventricular cyst	2
Hydrocephalus	3
SECTL	1
Calcified lesions	1
Drugs	
AED	5
Albendazole (postpartum)	1
Albendazole (pregnancy)	1
Praziquantel (pregnancy)	1
Praziquantel (postpartum)	1
Pregnancy outcome	
Normal delivery	6
Died	1
Seizure outcome	
Good	4

(SECTL-single enhancing computerized tomography lesion, AED-antiepileptic drug).

[a] (Bazley 1972, Forsbach *et al.* 1976, Kurl and Montella 1994, Paparone and Menghetti 1996, Suarez and Iannucci 1999, Torsone and McMahon 2000, Thakur *et al.* 2001).

in the brain. Cysticidal drugs were used either during pregnancy or postpartum in four patients. Most of them had normal delivery and good seizure outcome (*table 3*).
Our data indicate that the seizure and fetal outcome were comparable to pregnant women with epilepsy due to other causes. There were no differences in maternal and fetal outcome between the two groups. The seizure outcome in patients with NCC is generally good. Nearly 85% of patients with SECTL have a good seizure outcome although recurrence of seizures occurs in 15% of the patients (Rajshekhar and Jeyaseelan, 2004). In this series, patients with NCC had better control of seizures before and during pregnancy as compared to the comparative subjects.
We acknowledge the limitations of our study. There were no patients who had new-onset NCC during pregnancy. We did not repeat neuroimaging in NCC patients who had had seizure recurrence during pregnancy. It is likely that we would have missed any new NCC lesions, which can reappear in the same site or in a different site, due to periodic release of parasitic antigen within the cyst (Rajshekhar 2003a).
We compared seizure control during pregnancy with the pre-gestational, baseline seizure frequency. Seizure control during pregnancy was recorded prospectively; the pre-pregnancy, baseline seizure frequency was documented retrospectively, which may have problems of recollection bias and lack of accuracy (EURAP 2006).
The comparative group was matched for age and parity; we did not take into consideration seizure classification or epileptic syndrome. The comparative group had a generalized epileptic syndrome or a localization-related epileptic syndrome in almost equal proportions. This variation in underlying epileptic syndromes in the comparative group needs to be borne in mind while interpreting the results.
The lack of differences in the maternal and fetal outcome could be due to a poor statistical power considering the few pregnancies involved and the low incidence of adverse outcome. With the present sample size, the data would be significant at a difference of 45% between the groups (power 80%, Type I error 0.05).
Even though NCC accounts for 34% of all active epilepsy in India, we had only 30 patients with SECTL out of 1071 registrations in the IREP. This can be attributed to the large number of patients (n = 738) enrolled from one centre (SCTIMST, Thiruvananthapuram) where NCC is uncommon (Rajshekhar *et al.* 2006, Kuruvilla *et al.* 2001).
The IREP is a hospital-based registry, which may not reflect the epilepsy patient in the community. It is difficult to ascertain whether the patients in the comparative group without neuroimaging had NCC or not. In a hospital-based study of the review of CT scans performed in non-seizure disorders (n = 4452), only 29 (0.65%) cases had lesions suggestive of NCC (Singh *et al.* 2000). Therefore, the possibility of NCC lesions in the comparative group without neuroimaging is remote. Despite these limitations, our study provides new information regarding seizure, maternal and fetal outcomes in women with NCC and pregnancy.
In conclusion, NCC is an uncommon cause of epilepsy in pregnant women in hospital-based pregnancy and epilepsy registries in India. There were no differences between NCC and the comparative group with regard to maternal and fetal outcome although there were significant differences in the demographic profile and epilepsy-related characteristics between the two groups. The seizure outcome was good in the NCC cohort both before, and during the pregnancy. Our findings need to be confirmed in a large cohort of women with NCC. □

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