

Twin birth and epilepsy: An expanded Indian study

S Jain DM, MV Padma DM, A Puri MCom, MC Maheshwari MD

Department of Neurology, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi, India

Abstract

Objectives and background: The reports suggesting factors associated with twinning as a cause for epilepsy among twins have recently been contested. We studied the occurrence of epilepsy among twins and non-twins with an aim to investigate the association between twinning and epilepsy. **Methods:** Probands with epilepsy and non-epileptic disorders were consecutively ascertained and the occurrence of twin births documented among their families. The prevalence of epileptic twins among unselected epilepsy probands was compared with the frequency of twin births in their families. Occurrence of epilepsies among twin and non-twin relatives of probands with epilepsy and other neurological disorders was also compared. **Results:** Twin births were more frequent in 3013 families of epilepsy probands as compared to 908 families of probands with non-epileptic disorders (1:123 vs. 1:204, $p < 0.001$). The prevalence of epileptic twins among an unselected sample of epilepsy probands (1:64) was similar to that of twin births in their families (1: 62). The occurrence of epilepsy among those born as twins versus all first-and second-degree non-twin relatives in epilepsy families was similar (1:56 vs. 1:71, p value not significant). None of the 248 persons born as twins in families of non-epileptic probands had epilepsy. **Conclusions:** Epilepsy in twins is largely not due to factors associated with twin birth. Perinatal factors have little bearing on the aetiology of common epilepsies in the community. The higher incidence of twins among epilepsy families may suggest a population association between twinning and epilepsy.

Key words: Twins, epilepsy, India

INTRODUCTION

Human epilepsies as a group are a good example of multifactorial genetic disorders. Major insults to the brain in the form of significant pre- and peri-natal events causing brain damage, serious head injury, stroke, severe brain infections and infestations are all known to result in the development of epilepsy. Twin pregnancies are associated with a greater risk of antenatal and peri-natal complications which have been attributed to be responsible for the higher incidence of epilepsy among those born as twins reported in a few studies including one from India.^{1,2} Based on the data from a community-based study of twins, Berkovic et al were the first to report that twins do not have an increased risk of seizures and suggested that peri-natal factors had little bearing on the aetiology of the common epilepsies in the community.³ In a preliminary study of twins born in families of 524 Indian probands with epilepsy, we found the prevalence of epilepsy among twin and non-twin relatives was comparable.⁴ Our observations

supported findings of the Australian study by showing that twin birth was not a major risk factor for seizures even in families of Indian probands with epilepsy.

We have been engaged in an ongoing effort aimed at investigating the reported association between twinning and epilepsy. Our previous report had the drawback of small numbers as it was based on the study of epilepsy and twinning among 524 Indian probands with epilepsy and their family members. We now report our results on the relationship of twinning and epilepsy among data collected on more than 90,000 individuals.

MATERIALS AND METHODS

The data included in this study have been taken from an ongoing study to look into the occurrence of seizure types in relatives of probands with different epileptic syndromes. All probands included have been taken from the out-patient clinics of the Neurology Department, Neurosciences Centre, All India Institute of

Medical Sciences (AIIMS), New Delhi. As reported earlier, probands with a confirmed diagnosis of their seizure types/epileptic syndrome have been included in the study.⁴ The epilepsy probands were ascertained irrespective of their twin status and the seizure types/epileptic syndromes were classified as per International Classification of Epileptic Syndromes.⁵

Family pedigrees were constructed for all probands (AP) to include all the first and second-degree relatives of the probands. Information on twin births in the families was obtained from probands and their accompanying relatives while collecting family data and was reconfirmed during a follow-up visit. In some families with twin births, the pedigrees were extended beyond the first and second-degree relatives. The entire family data was rechecked and confirmed by the same person on both occasions (SJ). Information on relatives affected with epilepsy was similarly collected and one person (SJ) examined all available affected relatives. All probands and affected relatives that were examined had at least one conventional scalp EEG. CT and MRI scans of the brain were done as and when clinically indicated. The seizure types/epileptic syndromes among relatives that were examined were also classified in the same way as was done for probands.

The family pedigrees of probands with all neurological disorders other than epilepsy were similarly constructed and information on twin births and epilepsy among their relatives was collected. In order to examine the relationship of twinning and epilepsy in these families, we compared: 1) frequency of twin births among

families of probands with epilepsy and other neurological disorders, 2) frequency of epileptic twins among consecutively ascertained probands with epilepsy (selected irrespective of their twin status) with the frequency of twin births in their families, and 3) occurrence of epilepsies in the twin and non-twin relatives of probands with epilepsy and other neurological disorders.

Chi square test with Yate's correction factor was used to compare the twin rates and other statistics related to twin births and epilepsies among the two sets of data.

RESULTS

We report data collected from 3,013 probands with epilepsy and 908 with other neurologic disorders. From their family pedigrees, we had information on 64,859 and 25,330 births respectively. The ratio of twin to total births in families of epilepsy probands was higher (1:123) compared to that among families of probands with other neurologic disorders (1:204, $p < 0.001$) (Table 1).

Among 3,013 epilepsy probands, 47 were born as twins (1:64). In their families, we had information on 65,387 relatives (64,859 births + 528 twin births). In families of epilepsy probands 1,056 of 65,387 persons were born as twins. Thus, 1 in every 62 persons in these families was born as a twin. The frequency of epileptic twins among consecutively ascertained probands with epilepsy selected irrespective of their twin status (1:64) was similar to the frequency of twin births in these families (1:62).

In families of epilepsy probands, there were 1,009 (1,056 total persons born as twins minus

TABLE 1: Twin births among Indian families of probands with epilepsy and other neurological disorders

Diagnosis in probands	Number of Probands	Family Data		
		Total Births	Twin Births	Ratio of total: twin births
Epilepsy	3,013	64,859	528	1: 123
Non-epileptic disorders	908	25,330	124	1: 204
p value				< 0.001

47 epileptic twin probands) non-probands twins. Epilepsy was documented in 18 of these 1,009 twin relatives. Thus, the frequency of epilepsy among twin relatives of epilepsy probands was 1:56. Information with regards to epilepsy was available on 15, 978 first-degree and 45, 397 second-degree non-twin relatives in these families. Among the non-twin relatives, 481 first-degree (1:33) and 382 second-degree (1:119) had epilepsy. The frequency of epilepsy among non-twin first-degree relatives of epilepsy probands was significantly higher compared to that among all twin relatives (1:33 vs. 1:56, $p < 0.05$) (Table 2). Further, the frequency of epilepsy among twin relatives was comparable to that among all first- and second-degree non-twin relatives (1:56 vs. 1:71, p value not significant). There were 4 "twin pairs" with epilepsy among 47 epilepsy probands born as twins compared to only 1 epileptic twin pair among 481 non-proband twin births among their relatives ($p < 0.001$).

In families of probands with neurologic disorders other than epilepsy, 65 of 6,887 (1:106) first-degree and 74 of 18, 225 (1:246) second-degree non-twin relatives had epilepsy. The frequency of epilepsy among non-twin relatives of non-epilepsy probands was significantly lower compared to that among non-twin relatives of epilepsy probands (Table 2). None of the 248

persons born as twins in these families had epilepsy.

DISCUSSION

The main strength of our study being data with regards to twinning and epilepsy on a large sample of carefully studied patients and their family members that is available for analysis. This data has been collected in a unique way from patients attending the Neurology out-patient clinics of a tertiary care super-speciality hospital in a developing country (India), where facilities like community-based twin registries are non existing. The other strong points of our study are: 1) uniform methodology adopted in construction of family pedigrees by one trained person (AP), and 2) confirmation and classification of data with regards to twinning and epilepsy also by one person (SJ).

We had earlier reported that frequency of twin births in families of 524 probands with epilepsy was comparable to the twin births among consecutive deliveries over a 3 years period in another government hospital in the same catchment area in New Delhi (1:99 vs. 1:75). Further, every 1 in 58 of probands with epilepsy was a twin while a twin was born in these families every 1 in 71 live births. The frequency of epilepsy in non-proband twin relatives was

TABLE 2: Incidence of epilepsy among twin and non-twin relatives of probands with epilepsy and non-epileptic disorders.

	Twins with epilepsy (ratio)	1° non-twin relatives with epilepsy (ratio)	1° + 2° non-twin relatives with epilepsy (ratio)	p value	
Families of epilepsy probands	18/1009 ^a (1:56)	481/15,978 ^b (1:33)	863/61,375 ^c (1:71)	a : b 0.05	a : c NS
Families of non-epilepsy probands	0/248 ^d	65/6,887 ^e (1:106)	139/25,112 ^f (1:181)	a : e < 0.01	
p value		b : e < 0.001	c : f < 0.001		

NS: Not significant

1°: First-degree relatives

2°: Second-degree relatives

1.5% compared to 2% among non-proband, non-twin relatives. Our data suggested that twin birth was not a major risk factor for seizures even in families of Indian probands with epilepsy.⁴

The twinning rates in community and hospital based series reported from India have varied from 1:68 to 1:118.⁶⁻¹⁷ On the other hand, the twinning rates in different populations have varied from 2 and 7 per 1,000 to 20 per 1000. Based on these data, the populations have been classified into three broad groups having low (2-7 per 1,000), intermediate (9-20 per 1,000) and high (>20 per 1,000) prevalence rates.¹⁸ The present study raises some interesting issues. The most important observation that we report is the significantly higher frequency of twin births in 3013 families of epileptic probands compared with those having non-epileptic neurological disorders (1:123 vs. 1:204, $p < 0.001$). Despite an extensive search of literature, we were unable to find such a study for comparison.

This higher incidence of twin births among families of epileptic probands compared to that among families of probands with other neurological disorders can not be explained only by an ascertainment bias (under reporting of twin births in the families of non-epileptic probands) as we used similar methodology and same persons were involved in construction of family pedigrees and data collection. This finding has thrown up some interesting and entirely novel issues: Can the presence of a particular disorder among probands influence the twinning rate among family members? A long list of factors like maternal parity, weight, age, height, social class, nutrition, smoking, fecundability, and fertility; seasonal variations and even familial tendencies are known to affect twinning rates.¹⁹ Our observation of a higher incidence of twin births among epilepsy families needs to be confirmed by similar studies conducted in other population groups. If valid, this observation could suggest a modest population association between twinning and epilepsy. The association between twinning within families and epilepsy could presumably be due to shared genetic and environmental factors but twinning is not directly associated with epilepsy *per se*.

In a much smaller study, we had earlier reported that twin birth is not a major risk factor for seizures even in families of Indian probands with epilepsy.⁴ Our results now of a much larger study on the incidence of epilepsy among more than 90,000 twin and non-twin relatives of probands with epilepsy and other neurologic

disorders provide strong support to the first community based report from Australia and our earlier findings stating twin birth as not a major risk factor for seizures.^{3,4} As reported earlier, in the present study also the frequency of epileptic twins among consecutively ascertained probands with epilepsy selected irrespective of their twin status (1: 64) was similar to the frequency of twin births in these families (1: 62). Further, the frequency of epilepsy among twin relatives was significantly lower compared to that among non-twin first-degree relatives of epilepsy probands (1:56 vs. 1:33, $p < 0.05$). Additionally, among all non-twin first- and second-degree relatives of epilepsy probands, the frequency of epilepsy was comparable to that among their twin relatives (1:71 vs. 1:56, p value not significant). None of the 248 persons born as twins in non-epilepsy families had epilepsy. As expected from the effect of genetic influence, non-twin relatives born in epilepsy families had higher incidence of epilepsy compared to non-twin relatives of non-epilepsy probands (Table 2).

Our results of a higher incidence of epilepsy among first-degree non-twin relatives compared to twin relatives of epilepsy probands and similar incidence of epilepsy among twin versus all first- and second-degree non-twin relatives in epilepsy families provide evidence against the previous reports of twins having a higher risk for epilepsy.^{1,2} None of the twin born in non-epilepsy families having seizures. Our data support the contention that epilepsy in twins is largely not due to factors associated with birth process associated with twinning. This is supportive of the hypothesis that perinatal factors have little bearing on the aetiology of common epilepsies in the community^{3,4}, even in the context of a developing country like India.

It is a well-known fact that almost two-thirds of the world's total population today lives in developing countries. This poses tremendous problems and is a big disadvantage for these countries. On the other hand, those from the developing countries can convert the apparent "disadvantages into advantages". The relatively preserved family structure and the socio-cultural norms in developing countries like India are factors that allow such data collection without too many problems. Family studies such as ours provide an innovative prototype for clinicians to study the role of various factors implicated in the causation of complex neurological disorders like epilepsy.

In conclusion, our study provides further support to reports delinking factors associated

with twin birth from the causation of epilepsy among twins. This is supportive of the hypothesis that perinatal factors have little bearing on the aetiology of common epilepsies in the community. Although our findings need to be confirmed in other similar studies, the higher incidence of twins among epilepsy families could be due to a modest population association between twinning and epilepsy.

ACKNOWLEDGEMENT

This study was supported by a research grant from the All India Institute of Medical Sciences, New Delhi (India).

REFERENCES

1. Churchill JA. The relationship of epilepsy to twin birth. *Trans Am Microsc Soc.* 1958; 83:118-20.
2. Sharma K. Higher risk of epilepsy in twins. *Indian J Pediatr* 1986; 53: 515-19.
3. Berkovic SF, Howell RA, Hay DA, Hopper JL. Twin birth is not a risk factor for seizures. *Neurology* 1993; 43: 2515-19.
4. Jain S, Jain Menka S, Padma MV, Puri A, Sen P, Maheshwari MC. Epilepsies among twins born in families of Indian probands with epilepsy. *Seizure* 1998; 7: 139-43.
5. Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; 30: 389-99.
6. Bildhaiya GS. A study of twin births. *Indian Pediatrics* 1978; 15: 931-34.
7. Das Chaudhuri AB, Basu S, Chakraborty S. Twinning rate in the Muslim population of West Bengal. *Acta Genet Med Gemellol Roma* 1993; 42: 35-9.
8. Dutta I. A study of twin births in Jabalpur City. *Indian J Pediatr* 1972; 39: 15-9.
9. Ghosh S, Ramanujacharyulu TKTS. Study of twin births in an urban community of Delhi. *Indian J Med Res* 1979; 70: 70-7.
10. Joseph B. Hazards of Multiple pregnancy. *J Obstet Gynecol India* 1964; 14: 118-27.
11. Junnarkar AR, Nadkarni MG. Incidence of multiple births in an Indian rural community. *J Epidemiol Community Health* 1979; 33: 305-06.
12. Park JE. Observations of twin births in Gwalior City. *Indian J Pediatr* 1966; 33: 39-43.
13. Patel VG, Patel BC. A review of the cases of multiple pregnancy. *J Obstet Gynecol India* 1962; 12: 677-90.
14. Rao PSS, Inbaraj SG, Muthurathnam S. Twinning rates in Tamilnadu. *J Epidemiol Community Health* 1983; 37: 117-20.
15. Shah SB, Patel DN. Twinning and structural defects. *Indian Pediatr* 1984; 21: 475-78.
16. Srivastav JR, Bhalla M, Bhalla JN. A study of twins. *Indian Pediatr* 1977; 14: 121-27.
17. Trivedi RR, Motashaw ND. Outcome of the second of twins in 583 twin deliveries. *J Obstet Gynecol India* 1965; 15: 591-98.
18. Little J, Thompson B. Descriptive Epidemiology. In: McGillivray I, Campbell DM, Thompson B, eds: *Twinning and Twins*. John Wiley & Sons Ltd, 1988: 37-66.
19. MacGillivray I, Samphier M, Little J. Factors affecting twinning. In: McGillivray I, Campbell DM, Thompson B, eds: *Twinning and Twins*. John Wiley & Sons Ltd, 1988: 67-98.