Original Article

Genetic epidemiology of epilepsy: A twin study

Krishan Sharma

Department of Anthropology, Panjab University, Chandigarh - 160 014, India.

The study explored the genetic susceptibility and prevalence of epilepsy in twins. The data on epilepsy were retrieved from the health records of 199 pairs of twins. Proband concordance rate in monozygotic (MZ) twins was four times more than that in dizygotic (DZ) twins (0.67 vs. 0.17). Three of 15 (20%) affected twin kinships had epileptic first-degree relatives. These findings indicated significant underlying genetic susceptibility to epilepsy with the Holzinger's heritability estimate being 0.45. The prevalence of epilepsy was similar in MZ (45.45), DZ (45.11) twins, and their non-twin siblings (47.60). In the general population from various nationalities, the mean prevalence rate of epilepsy varied from 5 to 17 per 1000. The appreciably higher prevalence rate in twin kinships could be attributed to peculiar development factors associated with the twinning process or the intrauterine environment of mothers having tendencies to bear twins. Of the genetic markers, PTC locus seemed to be associated with the susceptibility to epilepsy. The allele frequency of non-tasters (t) seemed greater in epileptic twin kinships (0.71) than that in the general population (0.53). The frequency of non-tasters was similar in MZ and DZ twins and singletons: 27.3%, 26%, and 27.7% respectively. The PTC data on the general population was based on a sample of 278 individuals.

Key Words: Twins, concordance, PTC locus, prevalence of epilepsy, heritability.

Introduction

Epilepsy is one of the most common neurological disorders affecting people across all nationalities. It presents an etiologic heterogeneity and multifactorial pathogenesis. Genetic factors play an important role in the determination of the idiopathic epilepsy, both partial and generalized.[1] Chromosomal, single gene (autosomal dominant, autosomal recessive, X-linked), mitochondrial and polygenic/multifactorial disorders have been associated with epilepsy.[2] There is a long list of diseases/disorders having epileptic seizure as phenotypic expression. In fact, disorders associated with more than 10 human chromosomes are linked with epilepsy.[3,4] A genetic missense mutation has also been associated with autosomal dominant nocturnal frontal lobe epilepsy.[5] Certain genetic markers have also been linked with epilepsy. For example, juvenile myoclonic epilepsy has been linked to the HLA loci on Chrhomosome 6.[6]

Besides genetic factors, a large number of pre- and perinatal factors, such as obstetric trauma, cerebral palsy, prematurity and neurological damage are widely believed to be important causes of epilepsy.[7-10] Human twins have to face a high frequency of such adverse perinatal events. They have also shown higher prevalence of epilepsy.[11,12] These observations have been contradicted on the basis of comparison of the prevalence of epilepsy in twins with that in their non-twin siblings.[13] These contradictory reports warrant further clarification on this issue. We shall endeavor to address this question on the basis of some additional data on epilepsy in twins from northwest India. Second, we shall analyze the concordance rates for epilepsy in monozygotic and dizygotic twins of the present series in the light of previous data. Third, the genetic structure of patients with different diseases is usually investigated to study the association between genetic markers and disease. A major locus for the ability to taste phenylthiocarbamide (PTC) has been demonstrated, with insensitivity determined by a recessive gene.[14] We intend to analyze gene frequency at the PTC locus in twins belonging to kinships afflicted with epilepsy in comparison with the general sample of twins and singleton controls from the same population.

Materials and Methods

The twin registry of the Department of Anthropology, Punjab University, Chandigarh has been maintained since 1975. Since then, it has been updated from time to time. Many of these twins were recruited in infancy and early childhood as part of a longitudinal study of their growth and development. They belonged to an urban

Krishan Sharma
Department of Anthropology, Panjab University, Chandigarh - 160 014, India. E-mail: neelamkuki@yahoo.com

population of Chandigarh. The zygosity determination of the same sexed twins was based on the similarity method for various genetic markers: A1A2B0, Rh, MN, Kell and Duffy blood groups, ABH secretion, PTC tasting ability, dermatoglyphics and photographs. However, all the twins were not typed for all the genetic markers. The zygosity based on a questionnaire administered to twins and their parents alone has been shown to give an accuracy of 95%.[15-16] So the criterion used for establishing the zygosity of the twins gives the probability of error of less than 3%.

The data on epilepsy was retrieved from the health history records of 199 twin pairs. They included 66 monozygotic (MZ) and 133 dizygotic (DZ) twin pairs. The epilepsy was defined as two or more clinical seizures not resulting from withdrawal of any drug or alcohol and not related to an acute metabolic event. All the recorded epileptic twins had histories of convulsions, and received medical treatment in different hospitals for epilepsy. The seizures were afebrile and included both partial and generalized. The onset of the disorder was before the age of 16 years.

PTC taste sensitivity was recorded by using the serial dilutions of freshly prepared solution of PTC as described by Harris and Kalmus.[17] Solution no. 1 had 1300 mg of PTC dissolved in one liter of water. Solution no. 2 was half as concentrated as solution no. 1 and so on till solution no. 13. Solution no. 0 (zero) indicated those individuals who showed no sign of taste sensitivity to any of the 13 solutions employed. The water employed for the serial dilutions was simple boiled tap-water. Distilled water, to which the people were not generally used to, was not used for serial dilutions. PTC taste sensitivity was recorded on 66 MZ, 75 DZ twin pairs (282 individuals) and 278 singleton individuals belonging to the same population. The individuals, including epileptic twins and their normal co-twins, with mental retardation or those who showed reluctance or fear to taste the PTC solution were omitted. Mentally retarded subjects tend to give inconsistent responses on the sorting test and a spurious excess of non-tasters among classified persons.[18]

Twin pairs having both individuals affected with seizures, were designated as concordant. Pair-wise concordance was estimated by the formula: C/C+D, where C and D were the number of concordant and discordant twin pairs. Case-wise concordance was calculated as 2C/2C+D. Pair-wise concordance rates for epilepsy in MZ and DZ twins were used to calculate the heritability index following Holzinger,[19] Hc = (CMZ-CDZ)/(1-CDZ), and Allen,[20] H'c = 1-CDZ/CMZ. The significance of differences between the frequency distributions was tested with the help of the Chi-square test.

Results

The concordance rates in MZ twins are higher than that in DZ twins (Table 1). Holzinger's heritability estimate (0.45) is lower than that of Allen's heritability estimate (0.82). Case-wise prevalence of epilepsy is similar in MZ (45.45) and DZ twins (45.11), while pair-wise prevalence rate is higher in DZ (82.71) than MZ (60.61) twins. Of the 15 affected twin families, three families/probands (20%) had affected first-degree relatives: 2 parents (a father and a mother) and one non-twin sibling (Table 2). The probands had 21 non-twin siblings, but only one (4.76%) was affected.

PTC thresholds data could be collected on 13 of 18 epileptic twins as per reasons recorded under 'Materials and Methods' (Table 3). Frequency of the non-taster allele (t) is significantly higher in MZ than DZ twins. Of the 13 epileptic twins, 7 (53.8%) were non-tasters. Similarly, 4/9 (44.4%) of their unaffected co-twins were non-tasters. The Chi-square test between affected twins and their unaffected co-twins for PTC tasting ability is statistically insignificant ($\chi^2=1.31, P>0.05$). Consequently, their data were pooled and 11 of 22 (50%) were found to be non-tasters, giving allele frequency of non-taster allele as 0.707. This frequency is 155% greater than that of the singleton population, 162.5% greater than that in MZ twins and 137% greater than DZ twins. Chi-square (χ^2) tests for tasters versus non-tasters are all insignificant, except between MZ and DZ epileptic twins ($P<0.05$). Chi-square tests for taste threshold distributions (TSNs) are significant in 2 of 5 comparisons, i.e. MZ twins versus controls, and DZ twins versus controls. These differences are predominantly because of the lower frequency of TSNs from 10 to 13 in case of controls. A larger sample may remove this disparity, because the Chi-square tests between tasters and non-tasters for these two comparisons are insignificant.

Table 1: Prevalence, concordance rates and heritability of epilepsy in twins

	MZ (N=66)	DZ (N=133)
No. of concordant pairs	2	1
No. of discordant pairs	2	10
Pairwise concordance rate	0.50	0.09
Proband concordance rate	0.67	0.17
Casewise prevalence rate per 1000	45.45	45.11
Pairwise prevalence rate per 1000	60.61	82.71
Holzinger's heritability estimate (Hc)	0.45	
Allen's heritability estimate (H'χ)	0.82	

Table 2: Frequency of some associated medical problems and affected/unaffected first degree relatives of twin probands with epilepsy

	N	%
Speech unclear/handicap	4	22.22
Mental retardation and speech unclear	3	16.67
Parents affected	2	6.67
Non-twin sibling affected	1	4.76
Non-twin siblings unaffected	20	95.24

Discussion

The results of the present study on concordance and heritability have been compared with the published literature[21-37] in Table 4. Holzinger's (Hc)[19] and Allen's (H'c)[20] heritability indices were not reported by the studies under review, but these have been calculated from their concordance rates for epilepsy in MZ and DZ twins. The magnitudes of Hc and H'c estimates do not coincide with each other. It would follow from this that the heritability index is formula-dependent, and at times may not give a correct estimate of the genetic determination of the trait studied. It is clearly evident from Table 4 that H'c overestimates the genetic com-

Table 3: Frequency distribution of PTC taste thresholds and allele frequency among twins, epileptic twins, their normal co-twins and singletons

Threshold	All twins				Epileptic twins				Normal co-twins				Singleton controls	
Solution No.	MZ		DZ		MZ		DZ		MZ		DZ			
(TSN)	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0	8	6.06	24	16.00	5	83.33	2	28.57	-	-	3	42.85	29	10.43
1	11	8.33	6	4.00	-	-	-	-	1	50.00	-	-	12	4.32
2	6	4.55	5	3.33	-	-	-	-	-	-	-	-	13	4.68
3	8	6.06	4	2.67	-	-	-	-	-	-	-	-	14	5.04
4	3	2.27	9	6.00	-	-	-	-	-	-	-	-	9	3.24
5	4	3.03	5	3.33	1	16.67	1	14.29	1	50.00	-	-	19	6.83
6	5	3.79	8	5.33	-	-	-	-	-	-	1	14.29	16	5.76
7	20	15.15	18	12.00	-	-	1	14.29	-	-	-	-	41	14.75
8	5	3.79	13	8.67	-	-	-	-	-	-	-	-	56	20.14
9	20	15.15	16	10.67	-	-	2	28.57	-	-	1	14.29	38	13.67
10	17	12.88	18	12.00	-	-	-	-	-	-	1	14.29	17	6.12
11	8	6.06	11	7.33	-	-	1	14.29	-	-	1	14.29	4	1.44
12	10	7.58	10	6.67	-	-	-	-	-	-	-	-	1	0.36
13	7	5.30	3	2.00	-	-	-	-	-	-	-	-	9	3.24
Total	132	100.00	150	100.00	6	100.00	7	100.01	2	100.00	7	100.01	278	100.02
Allele frequency														
T		0.478		0.490		0.087		0.465		0.293		0.345		0.474
t		0.522		0.510		0.913		0.535		0.707		0.655		0.526
													MZ vs. Controls	DZ vs. Controls
χ^2 (Tasters vs. Non tasters)		2.02				3.90*					0.02	0.00		0.15
χ^2 (TSN vs. TSN)		19.85				4.01					9.03	53.50*		46.62*

*P<0.05.

ponent in the majority of cases.

The heritability estimates (Hc) for epilepsy in the above reviewed studies are strong with an average of 0.46 and standard deviation of 0.24. The results of the present study, with a heritability estimate of 0.45, are in perfect agreement with the average heritability calculated from the published data. A high standard deviation indicates that heritability indices from various studies vary widely. Several causes may be listed to explain these differences, which include ascertainment bias, unreliable self-reports in community-based studies and level of expertise in epilepsy diagnosis. To illustrate this point further, Table 4 shows that two studies[34,35] recorded considerably lower magnitudes of concordance and heritability rates. Despite this fact, both the studies concluded that genetic factors had a role in the expression of epilepsy and febrile seizures. Sillanpaa et al[35] attributed the lower heritability mag-

Table 4: Comparison of pair-wise concordance, heritability of epilepsy/seizures with the published literature from different nationalities

Reference	Source of twins	Seizure types	No. of pairs	Pair-wise concordance rate		Heritability estimates	
				MZ	DZ	Hc	H'c
Rosanoff et al. (1934)[21]	Hospital	Unknown	107	0.52	0.11	0.46	0.79
Conrad (1935)[22]	Mental hospital	Unknown	157	0.67	0.03	0.66	0.96
Inouye (1960)[23]	Hospital/referral	All	40	0.54	0.07	0.51	0.87
Marshall et al (1962)[24]	Hospital	Unknown	173	0.37	0.04	0.34	0.89
Braconi (1962)[25]	Referral	All	51	0.80	0.32	0.71	0.60
Harvald and Hauge (1965)[26]	Birth records	Unknown	127	0.37	0.10	0.30	0.73
Lennox and Lennox (1965)[27]	Referral	All	225	0.62	0.15	0.55	0.76
Vercelletto and Courjon (1969)[28]	Hospital	Afebrile	18	0.71	0.25	0.61	0.65
Badalyan et al (1970)[29]	Hospital	Unknown	35	0.80	0.05	0.79	0.94
Gedda and Tatarelli (1971)[30]	Hospital	Afebrile	45	0.95	0.15	0.94	0.84
Schiottz-Christensen (1972)[31]	Birth records	Febrile	64	0.31	0.07	0.26	0.77
Lennox – Buchthal (1973)[32]	Referral	Febrile	65	0.68	0.13	0.63	0.81
Berkovic et al (1990)[33]	Twin register	Afebrile	21	0.69	0.25	0.59	0.64
Corey et al (1991)[34]	Twin register	Afebrile	280	0.12	0.03	0.09	0.75
Corey et al (1991)[34]	Twin register	Febrile	252	0.19	0.06	0.14	0.68
Sillanpaa et al (1991)[35]	Twin register	Unknown	316	0.03	0.01	0.02	0.67
Ottman (1992)[36]	Community based data	Unknown	47	0.35	0.04	0.32	0.89
Berkovic et al (1998)[37]	Referral	Afebrile	171	0.46	0.11	0.39	0.76
Berkovic et al (1998)[37]	Twin register/referral	Febrile	82	0.41	0.07	0.37	0.83
Pooled (Total)	—	-	2276	0.50	0.11	0.46	0.78
Present Study	Twin register	Afebrile	18	0.50	0.09	0.45	0.82

nitude to selection bias due to more frequent migration among healthy members of discordant twin pairs.

The second major finding of the present study is that the prevalence of epilepsy is similar in MZ and DZ twins. In the literature, Ottman[36] found an association between MZ twinning and epilepsy. Berkovic et al[13] observed higher prevalence in MZ (41) than DZ (36) twins, though they found the differences between the two rates statistically insignificant ($P>0.1$). On the contrary, Rudensakara[38] found association of epilepsy with DZ twinning. The term prevalence with reference to twinning, in the literature, refers to the case-wise prevalence rate. In fact, the pair-wise prevalence rate is more appropriate for comparing the prevalence of disease/traits between zygosities. In the present study, the pair-wise prevalence of epilepsy is greater in DZ (82.71) than in MZ (60.61) twins.

Let us now compare the prevalence of epilepsy in twins with that in the general population. The prevalence rate is higher in twins than in the general population. Further, the prevalence rate is higher in developing countries than in developed countries.[39] The published literature on the prevalence of epilepsy in various countries was reviewed and the summary of the results is presented in Table 5. The prevalence rate in South Asia seems comparable with that in Europe and the USA though it is slightly higher in the former. The prevalence in Africa and Latin America is much higher. One would have expected that the prevalence of convulsive disorders would have greatly altered after the Second World War. Since then better obstetric and neonatal care, liberal use of antibiotics would have reduced the environmental causes of epilepsy, while leaving genetic causes unaltered. This has not happened as even in the USA, the prevalence of epilepsy has increased over the last 50 years or so.[40] It only indicates that new environmental stimulants have replaced the older factors. The prevalence rates given in Table 5 are much lower than that in twins. Similar results were reported earlier on the basis of a slightly smaller sample.[12] Since these observations have been contradicted,[13] the issue needs more critical analysis and also clarification. One way to crack the waxed problem, is to compare the prevalence rates in twins with that in their non-twin siblings.[13] Following this approach, we analyzed the prevalence of epilepsy in non-twin siblings of the affected twins. Of such 21 non-twin siblings, one was found to be affected. On the basis of these results, one can conclude that in the epileptic twin kinships, twins are not at a higher risk for epilepsy than their non-twin siblings. Similar results were reported by Berkovic et al.[13] They reported that the frequency of all seizures was 29/751 in non-twin siblings (3.9%) and 42/1092 in twins (3.8%) and the two rates are similar. By comparing the two studies, one should reach the conclusion[13] that twins do not have an increased risk of seizures than their non-twin siblings. However, these results cannot be extrapolated to state that twins do not have greater risk of epilepsy than the general population. Such a statement would not be true as there is overwhelming and infallible evidence against this. From the data presented by Berkovic et al,[13] the prevalence of seizures in twins and their non-twin siblings is 38 and 39 respectively per 1000. Corey et al[34] conducted a detailed survey of 14383 pairs of twins in the year 1982-83 in Virginia and Norwegian twin panel and found 536 pairs with a history of seizures, giving the prevalence rate of 37.27 per 1000. These prevalence rates are about seven times greater than those observed in the general population, which has an average of 5.04 in Europe and USA. How do we account for such huge differences in the prevalence of epilepsy in twins and in the general population? On the other hand, similarity in the prevalence of epilepsy in twins and non-twin siblings of the affected twins can easily be explained. The primacy of genetic factors in the etiology of epilepsy is an established fact as already discussed. Twins and their non-twin siblings share 50% genes in common and thus if twins are affected then the chances of their siblings being affected increased proportionately under the genetic hypothesis. In affected twin kinships, theoretically, the frequency of affected non-twin siblings is expected to be similar to that of dizygotic concordance provided the twinning condition does not provide an additional risk. There is another unique characteristic of the Australian data[13] that shows higher prevalence of epilepsy in non-twin siblings of the affected twins (12%) than the overall dizygotic concordance rate (9%), though the differences are statistically insignificant ($P>0.10$). This rate is about 2.5 times higher than that observed in our sample. To conclude, a critical review of the published data as well as the present study unambiguously show that the prevalence of epilepsy is higher in twin kinships than in the general population. An additional evidence to the above conclusion is provided by a study[41] reporting an excess number of twins (6%) among epileptic children than the frequency of twins in the same population (2%).

There can be various explanations to the above conclusion of higher prevalence of epilepsy in twin kinships. The intrauterine environment provided by the mother with the tendency to bear twins contributes towards higher risk factors for epilepsy through cerebral palsy or neurological damage. An association between twinning and cerebral palsy is well established.[9] The second plausible explanation is the biological basis of association between twinning and epilepsy phenomena as indicated earlier.[12,36]

No previous attempt has been made to study the association between the PTC locus and epilepsy in twins. The non-

Table 5: Prevalence of epilepsy in countries/continents

Countries/ Continents	No. of studies	Prevalence rate per 1000	
		Mean	S. D.
Africa	17	16.92	13.67
Latin America	12	16.60	5.45
India and Sri Lanka	11	5.93	3.14
Europe and U.S.A.	9	5.04	1.92

taster phenotype is a recessive character. Taste threshold distributions are dichotomized at their antimode. The first distribution till antimode belongs to non-tasters and the second one to tasters. Antimode usually varies from TSN 3 to 5. Consequently, there is an overlap between tasters and non-tasters with the possibility of a small proportion of individuals being classified as tasters or non-tasters. In the present study too, we find differences between the zygosities for the antimode. Since the difference is minuscule, it may be attributed to random differences in the sex composition of the samples as females are more sensitive than males in their tasting ability to PTC.[42] The results of the present study on the distribution of taste thresholds of epileptic twin kinships are very curious. There is an excess of non-tasters among epileptics than controls. The non-taster epileptic twins have thresholds of zero or one, while the other categories i.e. TSN 2 to 4 being almost missing. However, there is a further need to confirm these findings on a larger sample of epileptic twins.

To interpret the above association, let us first examine the utility of the PTC locus. PTC is an artificial chemical compound which does not exist as such naturally. It tastes bitter to tasters due to the presence of a thiocarbamide group.

In nature, there are a large number of edible plants belonging to the genus *Brassica,* which have antithyroid compounds like thiourea, thio-oxazoline and thiothiazoline and these contain the thiocarbamide group as does PTC.[43] So the ability to taste these compounds is correlated with the ability to taste PTC.[44] By implications from above, it will follow that taste sensitivity to PTC measures an individual's sensitivity to naturally occurring antithyroid compounds. So, PTC taste polymorphism has been seen as an oral rejection mechanism for the avoidance of naturally occurring antithyroid compounds.[45] According to this hypothesis, tasters will consume less of these food articles and thus minimize the stress on the thyroid gland. On the contrary, non-tasters of PTC will risk ingesting more of such food items and thus place themselves under greater thyroid stress. Mourant[46] envisaged the existence of balanced polymorphism at the PTC locus, based on the levels of iodine and thyroid inhibitors in the diet, such that if iodine was deficient or inhibitors in excess then tasters would be favored selectively, while if there was an excess of iodine or lack of inhibitors, non-tasters would be favored.

In the light of the above theoretical background, the diet history of the people of northwest India was evaluated. It reveals that the intake of vegetables belonging to the genus *Brassica*, e.g., cabbage, cauliflower, turnip, *Brassica* leaves, increases manifold during the winter season. In fact, these vegetables are eaten almost daily. The non-tasters tend to eat these vegetables in greater quantity and frequency, thus increasing the thyroid stress, especially during the winter seasons. These food habits have become part of their culture and are prevalent for centuries. In such a scenario, natural selection will favor tasters over non-tasters. Hence, we have a greater frequency of tasters in this region and there are no differences between twins and singletons for the frequency of tasters and non-tasters.

Now, the association between epilepsy and higher frequency of PTC non-tasters among epileptic twins may be explained by framing the hypothesis that non-tasters and less-sensitive tasters in this region, being under greater thyroid stress, are more prone to neurological injuries/infections than tasters who are more buffered and have an adaptive advantage because thyroid hormone stimulates the development of neurons (brain cells) in the central nervous system and speeds up both the brain's growth rate as a whole and the differentiation of its specific centers and pathways. There is evidence that PTC tasters manifest greater visual-motor maturation, while non-tasters show deficiency for this neurological developmental trait.[44] The non-taster developing fetuses may be at greater risk of neurological damage by naturally occurring thyroid inhibitors in the let of non-taster mother. In such a compound situation, there will be higher risk of cerebral palsy in the non-taster developing fetuses, which makes them more susceptible to epilepsy. These investigations are being extended to a large sample of singleton epileptic patients.

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Erratum

The title of the article "Sarcoglycanopathies: An enigmatic form of muscular dystrophy - A report of 7 cases" published in Neurology India (2004 Oct;52(4):446-449) should read as "Sarcoglycanopathies: A clinicopathological study of 13 cases".