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Prevalence of some risk factors in children with epilepsy compared to their controls☆

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Summary

Aim: The goal of this case–control study was to identify the significance of certain risk factors for epilepsy in Turkey.
Method: A total of 805 cases, aged 1–16 years, followed-up for epilepsy at the Pediatric Neurology Department and a control group consisting of 846 age-matched cases without epilepsy were included in the study. The risk factors examined were gender, neurological impairment, febrile convulsion, head trauma, central nervous system infections, parental consanguinity, family history of epilepsy, prenatal and natal risk and newborn jaundice. Data regarding the investigated epilepsy risk factors were obtained through a questionnaire via personal interviews and the medical records and were assessed using univariate and multivariate analysis.
Result: Univariate analysis showed an increased risk for epilepsy with a history of atypical febrile seizure (21.97-fold), severe and moderate head injury (27.76- and 7.09-fold respectively), CNS infection (4.76-fold), history of epilepsy in first-, second- or third-degree relatives (6.42-, 3.09- and 2.66-fold, respectively), presence of maternal hypertension (4.31-fold), an apgar score $\leq$6 at any time (7.78-fold) and

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neonatal jaundice (3.12-fold). Abnormal neurological signs increased the epilepsy risk 5.92 times in univariate analysis and 30.26 times in multivariate analysis.
Conclusion: The most important risk factors for epilepsy in this study were neurological impairment, history of atypical febrile seizures, severe head injury and a low apgar score. Other important risk factors were moderate head trauma and a history of epilepsy in the family.

Introduction

Epilepsy is one of the most common neurological disorders in childhood.[1] The cumulative lifetime incidence of epilepsy is 3% and more than half of the cases begin in childhood.[2] There are several population-based studies of epilepsy, but there are no specific studies identifying the characteristics and risk factors of epilepsy in Turkey.[3–5] Defining epilepsy risk factors will contribute significantly to understanding epilepsy pathogenesis and treating epilepsy.[6] Despite new diagnostic techniques such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET), only one third of the patients with newly diagnosed unprovoked seizures receive an etiological diagnosis.[7] Etiological factors for childhood epilepsy are different from those for epilepsy occurring later in life.[8,9] In children, perinatal insults, developmental deficits, genetic factors, degenerative CNS or other malformations and perinatal events (i.e., asphyxia and CNS hemorrhage) are all often identified as possible causes of epilepsy[7,10–15] whereas cerebrovascular and degenerative causes have become recognized as possible causes in older age groups.[16,17] CNS infection and head trauma may occur at any age.[18–20]

The prevalence of epilepsy is higher in developing countries when compared with developed ones. The incidence of epilepsy is 3 per 1000 in Italy,[21] 8 per 1000 in Turkey,[3] and 22.2 per 1000 in India.[22] However, the incidence is 9 per 1000 in Japan, a developed country.[23] The degree of development of a country is therefore not the only determinant of epilepsy incidence. The incidence of epilepsy is directly related to the incidence of epilepsy risk factors.[8,9]

In the present matched case–control study, we attempted to identify some possible risk factors for childhood epilepsy in Turkey for the first time.

Materials and methods

Study population

The patient group consisted of patients diagnosed with epilepsy between 1999 and 2005 at the Pediatric Neurology departments of Gazi University Medical Faculty and Dr. Sami Ulus Pediatric Diseases Training and Research Hospital. The control group consisted of patients followed-up at the general pediatric outpatient department of Gazi University Medical Faculty, the department where they had first presented at. All neurological disorders except epilepsy were included in the control group. The control subjects had completed the same number of years as the 10 cases according to the calendar year. We did not match for sex to observe the power of gender as a risk factor. Only index patients from each family were included in the study.

Sample and sample size

The frequency of the epilepsy risk factor with the lowest OR (1.3) in the patient–control group was calculated by using a sample size of 743 patients–743 control subjects with 95% CI and 95% power. Data collection continued for a year. A total of 848 patients and 925 control subjects were reached. A total of 43 patients and 78 control subjects with inadequate data for various reasons (refusal to participate, not being able to provide birth or hospital records, unreliable data, etc.) were removed from the study. The analysis was performed on 805 patients and 846 control subjects.

Definition

Epilepsy was defined as two or more afebrile seizures not associated with acute CNS insult and not occurring within a 24-h period.[24] Seizure type description followed the criteria of the International League Against Epilepsy.[25] *Neurological impairment*[13,26] was defined as any detected and specified deviation from what was considered normal by the examining pediatrician. Mental retardation (MR) was defined according to WHO as an IQ $\leq$ 70 present before the age of 18 years. The *Denver developmental test II* is an auxiliary text to be used on children aged 0–6 years who are apparently healthy to determine developmental problems.[27,28] *Febrile seizures* were defined as seizures occurring between the age of 3 months and 6 years, with no previous afebrile seizure (except

neonatal) and associated with fever but with no evidence of intracranial infection of other recognized acute neurological illness.[15] A febrile seizure was considered atypical when one or more of the following characteristics were present: prolonged (more than 15 min); focal (or partial); or multiple (more than one seizure in 24 h).[29] *Head trauma* was defined by at least one of the following: loss of consciousness because of brain injury, posttraumatic amnesia or evidence of skull fracture. Head trauma was graded as severe (brain contusion, intracerebral or intracranial hematoma, 24 h of either unconsciousness or amnesia) or moderate (skull fracture or 30 min to 24 h of unconsciousness or amnesia).[20] *CNS infection* was considered to be present in meningitis or encephalitis patients with an inflammatory cell response shown on lumbar puncture (LP).[30] Aseptic meningitis patients were not included in the study. *Parental consanguinity* in patients and controls was classified into two categories: (a) first cousins including double first cousins and (b) other relations which included first cousins once removed and second cousins once removed.[2] *Family history of epilepsy* was classified into three categories: (a) first-degree relatives for parents or siblings, (b) second-degree relatives for grandparents, aunts, uncles, nephews, nieces, (c) third-degree relatives for first cousins. *The prenatal period* was the time between the first day of the last menstruation up to the onset of labor starting the delivery. *The perinatal period* was from the start of labor, through delivery, and up to the end of the first week after delivery. A mother was considered to have *hypertension* if her blood pressure during pregnancy was $\geq$140 mmHg systolic or $\geq$90 mmHg diastolic on two separate occasions. *Infection during pregnancy* was diagnosed for events with symptoms and signs typical of systemic infection disorders (e.g., fever irrespective of whether the causative agent was identified). The presence of a neonatal complication was based on an *Apgar score* $\leq$6 at any time. *Hyperbilirubinemia* in the newborn full-term infant was defined as serum bilirubin $>$200 mM.[7]

Data collection

The data of the patients and controls were obtained with a prepared and structured questionnaire through personal interviews with the patients and their legal guardians after an informed consent was signed. The medical records were then reviewed. All patients were examined by a pediatric neurologist. Control subjects older than 7 years were subjected to a reading test, writing test and arithmetic test and the results compared with their age group. The IQ value of 34 control subjects whose scores were lower than their age group was evaluated. The first IQ value was taken into account for those patients who had been diagnosed with epilepsy before the study started. The cases less than 7 years old found to be normal following a neurological and physical examination were re-evaluated with the Denver developmental test II.

Differentiating aseptic meningitis from encephalitis is quite difficult. Patients where it was not possible to differentiate encephalitis from the case reports were included in the study as CNS infection being present.

The data were collected as male gender (no/yes), abnormal neurological sign (no/yes), febrile seizures (no/yes (simple/atypical)), head trauma (no/yes (severe/moderate)), CNS infection (no/yes), consanguinity (no/yes (first cousin marriage/other relations)), epilepsy in the family (no/yes (first-degree/second-degree/third-degree)), pre- and perinatal risk factors and neonatal jaundice (no/yes (hypertension/infection during pregnancy/apgar $\leq$6 at any time/neonatal jaundice)).

Statistical analysis

The collected data were coded and entered into the SSPS for Windows, Version 10.0, statistical package software program. Univariate analysis (chi-square) was carried out to determine factors influencing the patient and control groups. The relative risks for factors included in the univariate analysis were estimated by odds ratio (OR) and the 95% confidence interval (CI) calculated. Variables significant at the 5% nominal level were considered for multivariate analysis by logistic regression backward: conditional. The factors included in this analysis were male gender (no/yes), neurological examination results (no/yes), febrile seizures (no/yes), head trauma (no/yes), CNS infection (no/yes), parental consanguinity (no/yes), epilepsy in the family (no/yes), pre- and perinatal risk factors and neonatal jaundice (no/yes).

Results

This study was carried out between January 2004 and January 2005 at the Pediatric Neurology departments of Gazi University Medical Faculty and Dr. Sami Ulus Pediatric Diseases Training and Research Hospital. The analysis was performed on 805 patients and 846 control subjects.

The epilepsy classification changed during follow-up in 34.8% of our epileptic patients. Some cases thought to be generalized epilepsy proved to be

Table 1 Neurological impairments in the control group children

Impairment (n = 46)	%
Motor disability	52.2
Mental disability	39.1
Speech disorder	34.8
Behavioral disability	30.4
Migraine	10.9
Deafness	4.3
Blindness	2.2
Any other neurological impairment	32.6

partial epilepsy over time. Some cases that are unclassified were later classified as generalized or partial epilepsy. In conclusion, the 805 epilepsy cases included in the study were classifed as partial in 581 (72.2%), generalised in 152 (18.9%) and unclassified in 72 (8.9%).

In the epileptic group, 25.8% had at least one neurological abnormality in addition to epilepsy while this rate was 5.4% in the control. Table 1 shows the neurological impairments in the control groups.

There was no statistically significant difference between the epileptic group and the control group for a family history of consanguineous marriage or those with a history of infection during pregnancy although the rates were higher in the epileptic group ($p > 0.05$). Severe head trauma and atypical febrile seizures were found to be highly correlated with epilepsy development. Table 2 shows the prevalence of epilepsy risk factors in the patient and control groups.

Gender seemed to be important as a risk factor by increasing risk for epilepsy 1.26-fold (OR = 1.26; 95% CI, 0.996—1.593) following logistic regression but the final analysis was interpreted as no statistically

Table 2 Prevalence of some risk factors in children with epilepsy compared to their controls

	Prevalence (%)		OR	95% CI	P
	Patients, n = 805	Controls, n = 848			
Male sex					
No	40.7	48.7	1		
Yes	59.3	51.3	1.38	1.13—1.69	0.001
Abnormal neurological signs					
No	74.2	94.5	1		
Yes	25.8	5.4	5.92	4.19—8.39	0.0001
Febrile seizure					
No	80.8	97.4	1		
Simple	6.3	1.9	4.04	2.22—7.46	0.0001
Atypical	12.9	0.7	21.97	9.24—55.80	0.0001
Head trauma					
No	90.6	98.9	1		
Severe	6.3	0.9	7.09	3.22—16.25	0.0001
Moderate	3.1	0.2	27.76	6.35—170.38	0.0001
CNS infection					
No	95.7	99.1	1		
Yes	4.3	0.9	4.76	2.10—11.19	0.0001
Parental consanguinity					
No	81.5	86.2	1		
First cousin marriage	8.2	6.4	1.31	0.89—1.93	NS
Other relations	10.3	7.4	1.43	1.0—2.04	NS
Family history of epilepsy					
No	77.5	94.6	1		
First-degree relatives	14	2.5	6.42	3.30—10.65	0.0001
Second-degree relatives	6	2	3.09	1.71—5.64	0.0001
Third-degree relatives	2.5	0.9	2.66	1.10—6.59	0.026
Pre- and perinatal risk and/or newborn jaundice					
No	75	94.6	1		
Hypertension	10.3	2.6	4.31	2.60—7.17	0.0001
Infection during pregnancy	1	0.2	4.24	0.84—28.93	NS
Apgar $\leq$6 at any time	10.1	1.4	7.78	4.08—15.13	0.0001
Neonatal jaundice	3.6	1.2	3.12	1.45—6.90	0.002

Table 3 Analysis of epilepsy risk factors by logistic regression analysis

	OR	95% CI	P
Male sex			
No	1		
Yes	1.26	0.996–1.593	0.054
Abnormal neurological signs			
No	1		
Yes	30.26	13.905–65.834	0.0001
Febrile seizure			
No	1.00		
Yes	8.52	5.247–13.842	0.0001
Head trauma			
No	1.00		
Yes	9.17	4.501–2420.74	0.004
CNS infection			
No	1.00		
Yes	2.6	1.020–6.677	0.045
Epilepsy in family			
No	1.00		
Yes	4.75	3.267–6.906	0.0001
Pre- and perinatal risk and/or newborn jaundice			
Yes	1		
No	4.21	2.708–6.534	0.0001

significant difference for gender as the p value was 0.054. Abnormal signs on neurological examination increased epilepsy risk 5.92-fold in univariate analysis and was the most important risk factor for epilepsy in the logistic regression model (30.26-fold). Table 3 shows the evaluation of epilepsy risk factors by logistic regression.

Discussion

The determination by a country of its own risk factors for epilepsy will make an important contribution to the fight against epilepsy in that country and also in other countries. This study is distinguished by having the largest sample size for determining epilepsy risk factors in our country.

Male sex has been reported as a possible risk factor.[3,14] Although this was observed during univariate analysis risk factors in this study, it was not confirmed in the multivariate analysis.

There was a strong correlation between the presence of a neurological abnormality and the development of epilepsy in our study, as the both childhood and adult studies.[16,20,31,32] The rate of neurological abnormality was 25.8% in our epileptic patients and 5.5% in the control group. Brorson and Wranne[33] found a similar neurological abnormality frequency of 25% in epileptic patients but did not identify 'clumsy children'. Braathen and Theorell[13] reported an incidence of any neurological abnormality of 35% and of mental retardation, by itself or together with other neurological abnormalities, of 28% in epileptic patients. These studies show the close association between neurological abnormality and epilepsy development and indicate that children with a neurological abnormality have a higher risk of experiencing an unprovoked seizure and, once they have one unprovoked seizure, of a second seizure. Multiple logistic regressions in our study have, as expected, shown that any neurological abnormality increases the risk of epilepsy development 30.26-fold (95% CI, 13.905–65.834). The risk of a second seizure in children with normal neurological examination results who have experienced a single cryptogenic seizure is 37%[34] and our study shows a much higher risk of a second seizure in children with normal neurological examination results who have had their first unprovoked seizure.

Although the prognosis is generally very good, people who have had febrile seizures have a higher risk of developing spontaneous afebrile seizures, which define epilepsy when they recur.[35] A history of febrile convulsions increased the risk of developing epilepsy 8.5-fold in our patients and this conforms to the results of previous reports.[15,36] The epilepsy risk in patients with febrile seizures was not uniform: only 1–2.5% of patients who had experienced simple febrile seizures developed epilepsy,[37–39] while those with one or more atypical features had a 6–50% risk.[39,40] Although these results are generally consistent with the results of our study, we found that simple febrile seizures increased the risk of epilepsy development 4.04 times. Genetic factors are known to play a role in the development of both epilepsy and febrile seizures.[41–43] The high rate of consanguineous marriages in our epileptic patients and genetic factors may be contributing to our high percentage although we could not demonstrate statistical significance. It is also possible that the witness's recollection of the events is incorrect when such data are collected and the resulting incidence may be higher than the actual rate.

The incidence of epilepsy after head trauma has been extensively studied in the children and adult patient.[19,36,44,45] These studies show a high risk of epilepsy after head trauma. Similarly in our study, children with a significant history of head trauma had a 9.17-fold risk of developing epilepsy compared to the control group. In Olmsted County, Annegers et al.[20] reported that 11.5% of persons developed epilepsy $\leq$5 years after head trauma, a higher percentage than found in the present study. Dauod et al.[15] reported that head trauma in children

aged 3 months—14 years increased the risk of epilepsy 4.6-fold compared to the control group. These varying results may be due to the geographical differences between the countries and the different methods. However, even more importantly, data obtained from the family in retrospective case—control studies may be subject to recall bias, especially in the control group accepted as normal.

The incidence of CNS infection is highest in children, although a second peak is note in the elderly population.[18] There was a history of CNS infection in 4.3% of our epilepsy patients and 0.9% of the control group. This result is similar to the 4% reported by Al. Rajeh et al.[46] except in Pakistan where it was present in almost 10% of the patients.[17] Multiple logistic regression in our study revealed that CNS infection increased the risk 2.4 times. Annegers et al.[45] reported that a history of aseptic meningitis did not increase the risk of epilepsy while meningitis increased the risk 5 times and encephalitis 16 times. A study by Rocca et al.[36] showed that encephalitis was a risk factor only for complex partial seizures while Daoud et al.[15] found a higher rate of CNS infection among epileptic patients than in the control group but there was no statistically significant difference.

A positive family history of epilepsy increased the risk of developing epilepsy 4.75 times in our study. These results have been confirmed by previous reports.[17,40,47,48] In an urban locality study in Iran, Asadi-Pooya and Hojabri[14] reported that a positive family history of epilepsy increased the risk of developing epilepsy 3.34 times. Daoud et al.[15] stated that while the risk was significantly higher for all categories of family history for patients as compared to controls, the risk contributed by consanguinity was not significant. Although we found a higher rate of consanguinity in our epileptic cases, we did not find a statistically significant difference with the control group. However, the genetic basis of some types of epilepsy is now well-known.[49] Genetically transmitted epilepsy might be expected to be high in countries where consanguineous marriages are common such as Turkey,[50] Jordan[15] and Pakistan.[17]

Hypertension developing before or during pregnancy increased the risk of epilepsy 4.31 times when compared with the control group in univariate analysis. This finding is consistent with the results of several studies investigating this risk factor.[7,51] Hypertension is regarded as a risk factor for possible silent cerebrovascular accidents causing seizures in adults, and especially in the elderly.[17] Although patients with a history of maternal infection were more common in the patient group, the difference was not significant. This is probably due to the fact that the risk increases only when the mother has very severe infection. Recent reports did not confirm any of the pre- and perinatal factors previously suggested by Degan,[51] especially when children with mental retardation and cerebral palsy are excluded.[15] However, we found that a history of low Apgar scores increased the risk of epilepsy development significantly. Recently, Sidenvall et al.[7] did not find respiratory distress syndrome (RDS) or asphyxia to be risk factors for development of epilepsy but a low Apgar score was found to be a risk factor. Neonatal jaundice has been previously reported to be found often in patients with mental retardation[52] or cerebral palsy.[53] However, only a few studies report an association between epilepsy and neonatal jaundice.[7] We found with univariate analysis that neonatal jaundice increased the risk of epilepsy development 3.12 times.

This study has two main limitations although it have a very large sample size. This study is not a population based case control study. It therefore does not represent the community, but represents the group it was concerned with. It is also possible that the witness's recollection of the events is incorrect when such data are collected and the resulting incidence may be higher than the actual rate.

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