

Epidemiology of first epileptic seizures in the northern Aegean island of Lesbos, Greece

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Abstract

We aimed at establishing the epidemiologic profile of first epileptic seizures (FES) in the Greek island of Lesbos. During a 1-year period (01/06/2010 to 31/05/2011), cases of FES admitted to the Lesbos General Hospital/addressed by general practitioners/private neurologists were prospectively identified. A total of 45 cases (30 males and 15 females; mean age \pm SD of 59.4 ± 28.4 and 58.9 ± 26.8 years, respectively), were collected. The FES incidence rate was 52.1 (95% CI 37-67) per 10⁵ persons. Provoked and unprovoked FES had an incidence of, 16.2 and 35.9 cases per 10⁵ persons, respectively. Following age-adjustment to the 2000 US census population, incidence rates of FES (all types combined) were, 40.5 (95% CI 28-56) per 10⁵ persons. Cerebrovascular disease (CVD) was the most prevalent etiologic factor. The present findings indicate a low-ranking incidence of FES in the studied population and highlight CVD as a leading causative factor.

Introduction

Population based studies on the incidence of epileptic seizures are scarce and comparability of their findings is often limited by methodological differences.¹⁻⁶ Several parameters, including socioeconomic variables and lifestyle factors have been implicated in apparent differences in the incidence of provoked and unprovoked epileptic seizures within and between various populations worldwide.⁷⁻⁹ Nonetheless, common themes that emerge from the preponderance of epidemiological evidence on epileptic seizures for populations with well-developed healthcare infrastructures

include a bimodal distribution across age groups and a predominance of unprovoked over provoked seizures.^{1,8}

Data on the incidence of epileptic seizures and prevalence of etiologic factors in Greece derive from a single prospective population-based study conducted on an island complex.¹⁰ The findings of this study indicated a relatively low incidence of unprovoked epileptic seizures.¹⁰ Given the paucity of epidemiological studies on the incidence of epileptic seizures in Greece, we conducted a prospective population-based study, to identify first epileptic seizures, their etiology and treatment, in a Greek island population. Our investigation focused on Lesbos since this island offered several advantages, such as an extended state health network and remoteness from the Greek mainland, limiting the potential for cross-border consultation. Every effort was taken to adhere to the guidelines of the International League against Epilepsy (ILAE) on epidemiological studies in epilepsy and epileptic seizures.¹¹

Materials and Methods

Lesbos is one of the largest Greek islands (1632 km²; coordinates: 39° 10' 00" N, 26° 15' 00" E). According to the 2011 National Census (Greek Statistics Agency, Pireus, Greece), the population of the island comprised of 86436 permanent residents, 43% residing in the capital city of Mytilini. According to National Census data, in 2011, the population of Lesbos was older than that of Greece. The proportions of people aged over 65 in, respectively, Lesbos and Greece were 23.4% and 19.5%. Lesbos has been a rather isolated island, at a travel distance of 9 hours by boat or 1 hour by airplane from the mainland. A single state general hospital offers primary, secondary and tertiary care. This local hospital is the obligatory intermediate station for emergency cases that can subsequently be transferred to central mainland hospitals. In rural areas health care is also provided by state Health Centers. The Health Centers offer primary care, sometimes even secondary care. More than 95% of the islands inhabitants have social insurance covering the cost of hospital admission and neuroimaging in public and private diagnostic centres.

All patients that were permanent residents and were referred during the one-year study period (01/06/2010 to 31/05/2011) with a diagnosis of first epileptic seizure were included. Permanent residents were defined as residents meeting the 2011 National Census criteria provided by the Greek Statistics Agency: *persons that have*

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been living in their usual place of residence for a period of at least 12 months prior to the date of registration or have arrived to their usual place of residence during the last 12 months prior to registration with the intention to stay at their new place of residence for at least one year. Cases were recorded prospectively using the following information sources: i) the General Hospital of Lesbos, including the Neurology and Emergency Departments; ii) the two neurologists working in the private health sector; iii) general practitioners of the four public health Centres; iv) general practitioners of rural services throughout the island of Lesbos. Cases of epileptic seizures were confirmed and classified according to ILAE guidelines.¹¹ Thus, seizures in close temporal association with an acute systemic, metabolic or toxic insult, or in association with an acute central nervous system insult were classified as provoked epileptic seizures. Seizures occurring in the absence of a potentially responsible clinical condition or beyond the time interval estimated for the occurrence of acute symptomatic seizures (typically, but not exclusively

seven days), were classified as unprovoked seizures. Unprovoked seizures were subdivided into three categories: those of unknown etiology (termed idiopathic or cryptogenic) and those associated with either a known static neurological condition or a progressive CNS disorder (the latter two categories termed remote symptomatic).⁸ Febrile seizures occurring in children and neonates were excluded from the present analysis.

Standardized recording forms were filled by the participating neurologists. Data retrieved incorporated patient sociodemographic characteristics, medical history, neuroimaging (CT and/or MRI), electroencephalographic (EEG) and blood test findings, as well as type and cause of seizure. Collected data were reviewed by two specialist epileptologists (S.G and A.S, study authors). The study protocol was approved by the Evaggelismos Hospital (No 38, 8-2-2010) and Lesvos General Hospital (No 35, 29-1-2010) ethics committees. All patients gave informed consent and the present work was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2008).

Incidence rates were calculated as the number of cases per 10⁵ inhabitants, and 95% confidence intervals (CI) were established using a Poisson distribution. To allow for comparisons with other population based studies, incidence was age-adjusted to the 2000 U.S Census population (US Census Bureau, Suitland, Maryland, USA), using the direct method, as described previously.⁵

Results

A total of forty-five cases of first (provoked and unprovoked) epileptic seizures in permanent residents were included. They were 30 males and 15 females with a mean age ± SD of 59.4 ± 28.4 and 58.9 ± 26.8, respectively. Neuroimaging was available in 86.7% (39 of 45 patients), EEG recordings in 17.8% (8 of 45 patients) and screening blood tests in all patients.

Incidence rates of (combined provoked and unprovoked) first epileptic seizures were 52.1 (95% CI 37-67) per 10⁵. Seizure incidence rates showed a bimodal distribution across age groups in with an initial peak at the youngest age group (0-9 years), followed by a decline in incidence rates and a steep increase at age groups of 60 years and over. Incidence rates in children (<18 years) were 35.4/10⁵. Figure 1 shows the age- and gender-specific incidence rates of first epileptic seizures. Incidence rates peaked at the age group of 80 years and

over in both males (335.3/10⁵) and in females (98.3/10⁵). Following age-adjustment to the 2000 US Census population, incidence rates were 40.5 (95% CI 28-56) per 10⁵ persons.

Unprovoked seizures (Table 1) accounted for the majority of cases (68.9%). Incidence rates of unprovoked and provoked first seizures were 35.9 and 16.2 cases per 10⁵ persons, respectively.

Following age-adjustment to the 2000 US Census population incidence rates for unprovoked and provoked seizures were 23 (95% CI 15-33) and 17 (95% CI 9-30), respectively. Cerebrovascular disease (CVD) was the most common etiologic factor for provoked seizures and for unprovoked seizures due to static neurological conditions (Table 2). Unprovoked seizures related to progressive disorders were main-

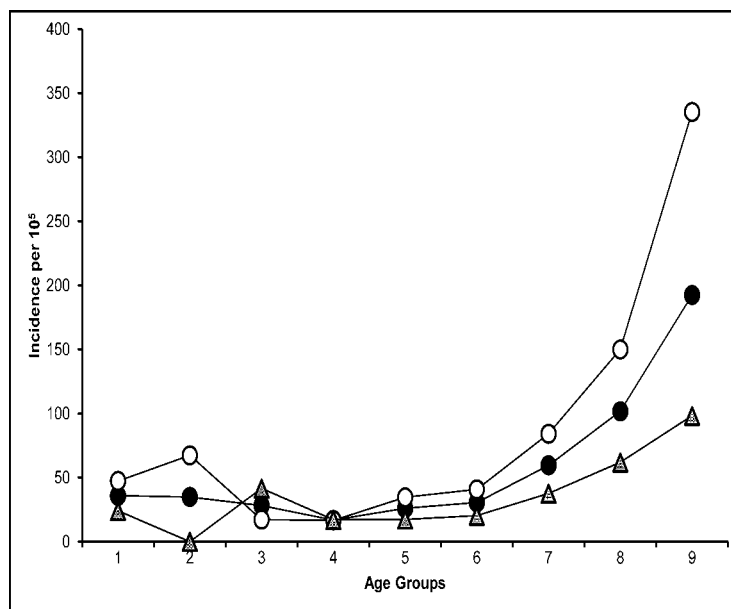


Figure 1. Age- and gender-specific incidence of first epileptic seizures in Lesvos, Greece (2010-2011). White dots: incidence rates in males; grey triangles: incidence rates in females; black dots: incidence rates in males and females combined. Age Groups: 1 = 0-9 years; 2 = 10-19; 3 = 20-29; 4 = 30-39; 5 = 40-49; 6 = 50-59; 7 = 60-69; 8 = 70-79; 9 = 80 years and over.

Table 1. Classification and crude incidence of first epileptic seizures.

Classification	N	Incidence (cases/10 ⁵)	%
Provoked seizures	14	16.19	31.11
Unprovoked seizures	31	35.86	68.89
Static disorders	19	21.98	(42.22)
Progressive disorders	6	6.94	(13.33)
Unknown etiology	6	6.94	(13.33)

Table 2. Etiologic classification of provoked and unprovoked first epileptic seizures.

Risk factor	Provoked		Unprovoked (stable disorders)		Unprovoked (progressive disorders)	
	N	%	N	%	N	%
Cerebrovascular	5	35.71	12	63.15	-	-
Metabolic	3	21.42	-	-	-	-
Tumor	3	21.42	-	-	5	83.33
Fever	1	7.14	-	-	-	-
Trauma	1	7.14	4	21.05	-	-
Encephalopathy	-	-	3	15.78	-	-
Undefined	1	7.14	-	-	-	-
Degenerative disease	-	-	-	-	1	16.66
Total	14	100	19	100	6	100

ly due to tumors (Table 2). Focal seizures with motor components with altered or retained awareness represented 31% of cases (N=14). Prominent myoclonic elements with generalized seizures were recorded in 4.5% of cases (N=2). Generalized seizures with insufficient data on focal or generalized onset accounted for 64.5% of cases (N=29). 97.8% of patients (N=44) with first epileptic seizures had no medical record of perinatal incidents requiring hospitalization, while two patients had a medical history of febrile seizures during childhood. Antiepileptic treatment following first seizures was given to 42 out of 45 patients (93.3%). Drugs used were: levetiracetam in 52.4% of cases, phenytoin in 31%, oxcarbazepine in 21.4%, lacosamide in 7.1% and valproic acid in 4.8%. Monotherapy and polytherapy was used in, respectively, 85.7% and 14.3% of treated cases. Polytherapy was used on recurrent seizures during hospitalization.

Discussion and Conclusions

Prospective population-based studies on the incidence of first epileptic seizures are scarce. Nevertheless, such studies can provide valuable insights for the identification of high-risk groups and development of preventive strategies.^{1,8} The present study investigated the incidence of first epileptic seizures, their etiology and treatment in the Greek island of Lesbos. An earlier prospective population-based study conducted in Greece, indicated a relatively low incidence of first unprovoked epileptic seizures in a Greek island complex (Corfu district).¹⁰ The epidemiologic profile of first epileptic seizures in the present study is comparable to that established in the majority of studies on populations covered by a well-developed healthcare infrastructure.^{1,8,12} Thus, the present results indicated a bimodal distribution in seizure incidence rates across age groups with an initial peak at the youngest age group (0-9 years), followed by a decline in incidence rates and a steep increase at age groups of 60 years and over. Additionally, the present findings showed a predominance of unprovoked over provoked seizures and a substantial male predominance in occurrence.

The incidence of first seizures (combined provoked and unprovoked) in the present study (52.1 per 10⁵) is comparable to that in other developed countries; nevertheless, higher estimates have been reported for populations in the United States, Western European countries and their overseas territories (range: 70.8-100.4 per 10⁵).^{1,8} The incidence of unprovoked first

seizures in the studied population (35.9 per 10⁵) is at the low end of the range of estimates established by previous studies following ILAE guidelines (range: 23 to 81/10⁵).^{1,8} Moreover, the incidence of provoked seizures (16.2 per 10⁵) represents one of the lowest estimates thus far reported.^{1,8} In this context it is noteworthy that cases related to common etiologic factors, such as drug and alcohol abuse and/or withdrawal,⁸ were not identified. While nearly all of the island's inhabitants have social insurance covering the cost of hospital admission, the possibility that sociocultural factors such as social stigma, contributed to the underreporting of cases related to toxic substances and alcoholism, cannot be excluded. On the other hand, CVD represented the most common etiologic factor of both provoked and unprovoked seizures; this finding appears consistent with a high burden of CVD in the studied population,¹³ as well as previous findings indicating that CVD is a significant cause of morbidity in Greece.¹⁴ Whether treatment of first seizures influences prognosis remains a topic of considerable interest and debate.^{8,15} A recent systematic review on treatment of first unprovoked seizures in adults has provided evidence that immediate antiepileptic drug therapy will reduce the risk of recurrence within two years but will not improve long-term prognosis for seizure remission.¹⁶ In the present study a very high proportion of patients received antiepileptic treatment following first seizures (93.3%). Moreover, analysis of treatment following first epileptic seizures indicated a clear trend for the prescription of newer antiepileptic medication (levetiracetam was given in the majority of cases).

The present findings, indicating a relatively low incidence of unprovoked epileptic seizures, are consistent with those in the only pre-existing epidemiological study in Greece.¹⁰ Nevertheless, incidence rates of provoked first seizures appear to be lower in the present study (Lesvos: 16.1 per 10⁵ vs district of Corfu: 27 per 10⁵). Moreover, in contrast to the earlier Greek study that showed a slight female predominance in first seizure occurrence, the present results indicated a substantial male one. An exceptionally high male to female incidence rate ratio of first seizures was previously reported on the island of Martinique and was speculated to reflect a leading role of male-related risk factors.⁴ The reasons behind the substantial male bias in first epileptic seizure occurrence in the present population remain unclear. Nevertheless, given that CVD was the leading etiologic factor, the present results appear consistent the preponderance of epidemiological evidence

indicating a male bias in stroke incidence.¹⁷ A male predominance in incidence and a prominent causative role for CVD in newly diagnosed epileptic seizures was previously detected in the population based study of Tchalla *et al.* (2011) that focused on elderly patients.¹⁸

Certain limitations of the present study need to be acknowledged. The limited observation period of one year, led to the detection of a small number of incident cases. Longer observation periods are clearly warranted to extend the present findings. Moreover, compared to other salient studies,^{5,9} the present findings incorporated fewer EEG recordings; this was due to the unavailability of such services in rural areas covered by health centers mainly offering primary care. In addition, the possibility that a number of first seizure cases escaped detection remains open. Thus, while every effort was taken to cover all potential reporting sources and adhere to recommended ILAE guidelines, a number of cases such as those seeking medical care in larger mainland centers (*e.g.*, surgical cases that developed postoperative complications) could have escaped detection. Moreover, given that the island of Lesbos lacks a pediatric intensive care unit, pediatric patients that were transported outside the study region for consultations could have escaped detection. In this context it is noteworthy that incidence rates in children appear lower than previous salient estimates.^{8,10,19,20}

In conclusion, the present findings indicate a low-ranking incidence of first epileptic seizures overall and a particularly low incidence of provoked first seizures in the studied Greek island population. CVD was the major etiologic factor for provoked and unprovoked first seizures.

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