

Newly-diagnosed epileptic seizures in three populations: Geneva (EPIGEN), Martinique (EPI MART), and the Reunion Island (EPIREUN)

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ABSTRACT – *Aim.* The objective was to analyse and discuss data from three studies of newly-diagnosed epileptic seizures (provoked and unprovoked) conducted in Geneva, Martinique, and the Reunion Island, in which the same methodology was used. *Methods.* We extracted data from three studies in which the incidence of seizures was estimated and aetiologies identified. Data was extracted and analysed using STATA. Group comparison was performed firstly for each study as a single group, and secondly by considering Martinique and the Reunion Island as an overseas group, in comparison with Geneva, considered as a mainland group. Uncorrected χ^2 was used and statistical significance (two-sided, $p=0.05$) was determined for each aetiology per cohort. *Results.* The incidence of newly-diagnosed epileptic seizures per 100,000 was 71.0, 80.6, and 100.4 in Geneva, Martinique, and the Reunion Island, respectively. A bimodal distribution and predominance of generalised seizures was noted. The male to female ratio was higher in Martinique (~ 2.0) than other populations (~ 1.5). Status epilepticus was noted in Geneva and more so in the Reunion Island. The incidence of provoked seizures per 100,000 was 25.2, 16.4, and 17.7, and for unprovoked seizures was 45.6, 64.1, and 81.2 in Geneva, Martinique, and the Reunion Island, respectively. There was a greater risk of provoked seizures in Geneva relative to the overseas group, which was due to tumours, use of toxic substances, and drug abuse. The risk of unprovoked seizures in Geneva was due to trauma and infections. In Martinique, alcoholism and HIV were foremost factors for provoked and unprovoked seizures, and

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stroke was an important aetiology in both Martinique (provoked seizures) and the Reunion Island (unprovoked seizures). *Conclusion.* The risk of provoked seizures was greatest in Geneva and risk of unprovoked seizures was greatest in the Reunion Island. Toxic substances, alcohol, infection, and trauma constituted major factors for epileptic seizures in Geneva, while alcoholism, HIV, and stroke were major factors in the overseas group. Relative eradication of tropical infections has paved a way for the emergence of non-communicable aetiologies (stroke, alcoholism). Males from Martinique demonstrated the greatest risk of epileptic seizures, signifying the importance of alcoholism, HIV, etc. Three steps should follow: follow-up studies (mortality), strong mechanisms for prevention (or control) of risk factors, guidelines on whether to treat or not.

Key words: epileptic seizure, Geneva, incidence, Martinique, Reunion Island

Epileptic seizures are either provoked or unprovoked. Provoked seizures (PS) are related to a relative structural or metabolic acute insult with which they have a characteristic and visible temporal relationship. Unprovoked seizures (UPS), on the other hand, do not have a clear temporal relationship with their underlying cause. This differentiation is important since the incidence, mortality, cause, onset age, and need to treat, vary (Jallon *et al.*, 2001; Hauser and Beghi, 2008) for these seizure types. Without doubt, the management of UPS is very important since they are very likely to develop into epilepsy. The management of PS is no less important but these are seldom indexed as a diagnosis and patients are rarely referred for neurological evaluation (Hauser and Beghi, 2008). Studies show that PS may present as status epilepticus, occur multiple times within 24 hours, or recur beyond 24 hours either as an acute seizure or UPS (Hesdorffer *et al.*, 1998; Leung *et al.*, 2010). There is also a high mortality risk either directly due to PS or due to their underlying cause (Loiseau *et al.*, 1990; Hesdorffer *et al.*, 2009).

Thus, it seems appropriate to evaluate a “complete seizure package” by including both PS and UPS in any given population. There are only a handful of reported studies in which this task has been undertaken in different populations using an identical protocol. Thus, a comparison between such studies is useful in order to draw any further conclusions. The objective of this study was to compare and evaluate the results of three comparable population-based cohorts conducted in Geneva (Switzerland), Martinique (France), and the Reunion Island (France), in order to generate further conclusions regarding provoked and unprovoked seizures in these populations.

Methods

We conducted an analysis of the results of three prospective population-based studies conducted in Geneva (EPIGEN, Switzerland) (Jallon *et al.*, 1997),

Martinique (EPIMART, France) (Jallon *et al.*, 1999a), and the Reunion Island (EPIREUN, France) (Mignard *et al.*, 2009). In these studies, the incidence rates were estimated and aetiologies identified with regards to newly-diagnosed epileptic seizures (PS and UPS). The Reunion Island and Martinique are overseas territories of France. Geneva is a French-speaking province in Switzerland. The study in Geneva was conducted during the human immunodeficiency virus (HIV) epidemic. The level of healthcare delivery system (including specialist care, encephalography, and neuroimaging) is of a high standard and comparable between these three populations; there was, for example, an available social security system for all subjects. As listed in *table 1*, along with many other recruitment sites, EEG labs were also engaged in recruiting participants. This was the case since, in these populations, any patient suspected to have an epileptic seizure would have had an EEG at one point or another. This also helped us to separate epileptic from index seizures. Standard definitions were used for defining PS and UPS, as well as the respective risk factors. Neonatal seizures (*i.e.* seizures occurring before one month) and febrile convulsions were excluded, as well as patients passing through the island. The classification according to the International League against Epilepsy was used for seizure classification, which divides seizures into generalised seizures, partial seizures, and unclassifiable seizures (ILAE, 1981). The aetiology of seizures was determined on the basis of medical history, neurological examination, EEG recording, and imaging, when conducted. We used the classification of risk factors, following the guidelines proposed by the Commission of Epidemiology and Prognosis of the International League against Epilepsy (ILAE, 1989). The categorisation of seizures was based on the presence or absence of a presumed acute precipitating insult, which allowed us to distinguish between provoked and unprovoked seizures. Provoked seizures are equivalent to acute symptomatic seizures or situation-related seizures.

Table 1. Characteristics of the three included studies.

Character	MARTINIQUE	GENEVA	REUNION ISLAND
Recruitment	- All neurologists, paediatricians, - ER practitioners 9 hospitals - 260 GPs	- Data from neurology neuropaediatrics, epileptology, EEG lab and psychiatric hospital; - 8 private neurologists	- Data from neurology and neuropaediatrics from 3 hospitals - GPs - 14 neurologists (public, private)
Diagnosis	Clinical+EEG+CT Chart review by epileptologist	Clinical+EEG+CT+MRI Chart review by epileptologist	Clinical+EEG+CT+MRI Chart review by epileptologist
Non-inclusion	Non-resident, febrile and neonatal seizures, <1 month age	Incomplete charts, febrile and neonatal seizures	Non-resident, incomplete case history, febrile and neonatal seizures, <1 month age
Classification	ILAE	ILAE	ILAE

CT: computerised tomography; EEG: electroencephalogram; ER: emergency room; GP: general practitioner; ILAE: International League Against Epilepsy; MRI: magnetic resonance imaging.

Single or recurrent unprovoked seizures may belong to two categories: remote symptomatic, of which there are two subtypes resulting from a stable condition or progressive central nervous system disorders, and seizures or epilepsies of unknown cause (idiopathic and cryptogenic). All clinical and EEG data of all studies were reviewed by a senior epileptologist. Charts containing inadequate, incomplete, unclear, or unsatisfactory data were excluded during all studies. All data regarding recruitment, diagnosis, non-inclusion, and classification are summarised in *table 1*. *Figure 1* depicts the geographic location of the three study locations.

Populations studied

The Reunion Island

The Reunion Island is a tropical French overseas territory, situated in the South Indian Ocean

(55.36°E/21.06°S) with a total area of 2,512 km². It is located about 200 km south west of Mauritius and 9,200 km from Paris. The majority of the population is ethnically mixed (53%) or European (23%) and the rest have diverse origins, predominantly Indian (Malabars, Muslims, Punjabi, etc.) and other minority groups belonging to China and African tribes. The active population works essentially in the tertiary sector and the unemployment rate is three-fold more (29.5%) than in metropolitan France (8.9%) (INSEE, 2010). The Reunion Island is largely urban with about 6% of the population living in rural communities (2009 data).

Martinique

Martinique is located in the eastern Caribbean Sea at 14°40'N/61°00'W with a total land area of 1,128 km². It is located along with Dominica (northwest), St Lucia (south), and Barbados (southeast) and lies about 7,000 km from Paris. The majority of the population is

**Figure 1.** Geographic location of Reunion Island, Martinique, and Geneva.

ethnically mixed (90.0%), European (5.0%), and Indian and Chinese (5.0%). The active population works in the tertiary sector and the unemployment rate is 26.3%. The level of care, which is of a high standard, and access to care is similar to that in metropolitan France. Martinique is largely urban with about 11.0% of the population living in rural communities (2010 data).

Geneva

Geneva is one of the provinces of Switzerland and has a total area of 282 km². The canton is surrounded on almost all sides by France. The majority of the population is largely international and 38.0% of the total population has a foreign origin. According to a national survey, 55.0% of the total population hold a non-Swiss passport. The unemployment rate is about 6.0%. The level of care and access to care is of a high Western European standard. Geneva is mainly urban with surrounding villages bordering France which are largely rural.

Methodology and data analyses

These three cohort studies were chosen because identical protocols and procedures were used. Data for each of these studies was extracted and documented

using Microsoft Excel. Data analyses were performed using version 8.0 of STATA. Group comparison of data was performed in various ways: firstly, each study was analysed as a single group, and secondly, data from the overseas population (Martinique and the Reunion Island) were combined to obtain a single “overseas group” and a group comparison was made with data from Geneva (considered as the mainland population). Uncorrected χ^2 was used and p (two-sided) was set at 0.05. Statistical significance was determined for each aetiology per cohort. For parameters for which group comparison was not possible or not performed, data was descriptively presented.

Results

Incidence (per 100,000) of all epileptic seizures (PS plus UPS)

The incidence of epileptic seizures (PS and UPS) varied between 71.0 in Geneva and 100.4 in the Reunion Island. The incidence in Martinique was between the two (80.6). The age-adjusted (US population) incidence varied from 69.4 in Geneva to 115.4 in the Reunion Island, and again, the incidence in Martinique was between the two (77.7) (*table 2*).

Table 2. Frequency and incidence rate (per 100,000) of provoked (PS), unprovoked (UPS) and total seizure types.

SEIZURE TYPE	Geneva (%)	Martinique (%)	Reunion Island (%)
Total PS	35.5	20.4	17.7
Total UPS	64.5	79.6	80.9
Stable UPS	25.2	23.9	33.9
Progressive UPS	9.9	5.5	3.0
Total Unknown UPS	29.3	50.2	44.0
<i>Idiopathic Unknown UPS</i>	6.6	8.0	6.7
<i>Cryptogenic Unknown UPS</i>	22.7	42.0	37.3
Unclassified	0	0	1.4
INCIDENCE PROVOKED AND UNPROVOKED			
TYPE	Geneva (%)	Martinique (%)	Reunion Island (%)
PS	25.2	16.4	17.7
Total UPS	45.6	64.1	81.2
Stable UPS	17.9	19.3	34.1
Progressive UPS	7.0	4.5	3.0
Undetermined UPS	20.8	40.4	44.2

Age and gender-specific incidence of epileptic seizures

These estimates are presented in *figure 2*. Males had a higher incidence of epileptic seizures than females in all three populations. The male to female ratio was 1.55 in Geneva and 1.56 in the Reunion Island. The ratio in Martinique was slightly higher (1.94) than in the other two populations. A bimodal distribution of incidence was noted across various age groups in all populations; peaking at a very young and then at a very old age.

Seizure type

Generalised seizures (GS) varied from 48.8% in the Reunion Island to 63.8% in Martinique, and 53.1% in Geneva. Most partial seizures (PS) were noted in Geneva (36.2%), followed by Martinique (8.4%), and the Reunion Island (8.2%). Secondary generalised PS were absent in Geneva and present in 16.5% in Martinique and 13.7% in the Reunion Island. Status epilepticus (SE) was noted in Geneva (5.4%) and the Reunion Island (8.5%). The percentage of unclassified and undetermined cases was 5.0, 11.3, and 19.3% in Geneva, Martinique, and the Reunion Island, respectively. Missing data was infrequent (0.3% in Geneva, 0% in Martinique, and 1.4% in the Reunion Island).

Provoked seizures (PS)

The incidence (per 100,000) of PS varied from 16.4 in Martinique to 25.2 in Geneva and the incidence in the Reunion Island was between the two populations (17.7). The proportion of PS was greatest in Geneva (35.5%), compared to Martinique (20.4%) and the Reunion Island (17.7%). These differences were statistically significant ($p < 0.0001$) (*table 2*).

Alcohol withdrawal and use of toxic substances and drug abuse constituted 50.4% of PS in Geneva, 41.2% in Martinique, and 27.4% in the Reunion Island ($p = 0.001$). Stroke was similarly frequent in Geneva (18.5%) and Martinique (20.6%) and was about two-fold higher than in the Reunion Island (10.4%); $p = 0.00001$. Trauma was significantly more frequent in Martinique (18.7%) and the Reunion Island (11.1%) than Geneva (2.0%); $p = 0.001$. Other aetiologies such as CNS infection, tumour, and metabolic disorder, as well as multiple aetiologies and post-operative cases, were individually infrequent and the differences were not statistically significant ($p = 0.16$). There were 0% unspecified aetiologies in Geneva and Martinique and 51.1% in the Reunion Island (*table 3*).

Upon comparison between the two overseas populations (*i.e.* Martinique and the Reunion Island), stroke was the only aetiology that was statistically significant

($p = 0.02$) between them. Upon comparison of mainland (Geneva) *versus* the overseas population, trauma (2.0% *vs.* 29.8%; $p = 0.00006$) was significantly less frequent in mainland compared to the overseas population. In contrast, the use of toxic substances and drug abuse (20.6% *vs.* 5.5%; $p = 0.00007$) and tumours (10.3% *vs.* 4.7%; $p = 0.05$) were more statistically frequent in mainland than the overseas population (*table 3*).

Unprovoked seizures (UPS)

The incidence (per 100,000) of UPS varied from 45.6 in Geneva to 81.2 in the Reunion Island, while the incidence in Martinique was between the two populations (64.1) (*table 2*).

Stable UPS

The incidence (per 100,000) of stable UPS was greatest in the Reunion Island (34.1), followed by Martinique (19.3), and Geneva (17.9). The proportion of UPS was greatest in the Reunion Island (33.9%), followed by Geneva (25.2%), and Martinique (23.9%); $p = 0.0009$. The predominant aetiologies in Geneva were stroke, perinatal injury, alcoholism, and trauma and constituted 81.0% of cases. These aetiologies constituted 85.1% cases in Martinique and 72.0% in the Reunion Island. Major differences in the frequency of these aetiologies were noted and those aetiologies in which the difference was statistically significant included stroke ($p = 0.06$) and alcoholism ($p < 0.00001$). The remaining aetiologies (malformation, CNS infection, encephalopathy, and undetermined or post-operative cases) were statistically insignificant (*table 3*). Upon comparison between two overseas populations, stroke (0.01) and alcoholism ($p = 0.00001$) were major aetiological factors, while a comparison between the overseas and mainland populations revealed the major aetiological factors to be trauma ($p = 0.06$), infection ($p = 0.08$), and alcoholism ($p = 0.0003$).

Progressive UPS

The incidence (per 100,000) of progressive UPS was greatest in Geneva (7.0), compared to Martinique (4.5) and the Reunion Island (3.0), and the proportion of UPS was similarly observed (9.9, 5.5, and 3.0%, respectively). HIV, degenerative disorders, and tumour constituted 81.4% of cases in Geneva, 93.9% in Martinique, and 69.4% in the Reunion Island. For 30.4% cases in the Reunion Island, aetiology remained unclassified. HIV was the only aetiology that was statistically significant ($p = 0.04$) between the three populations (*table 3*).

Upon comparison between the two overseas populations, HIV (0.01) was the only aetiological factor that

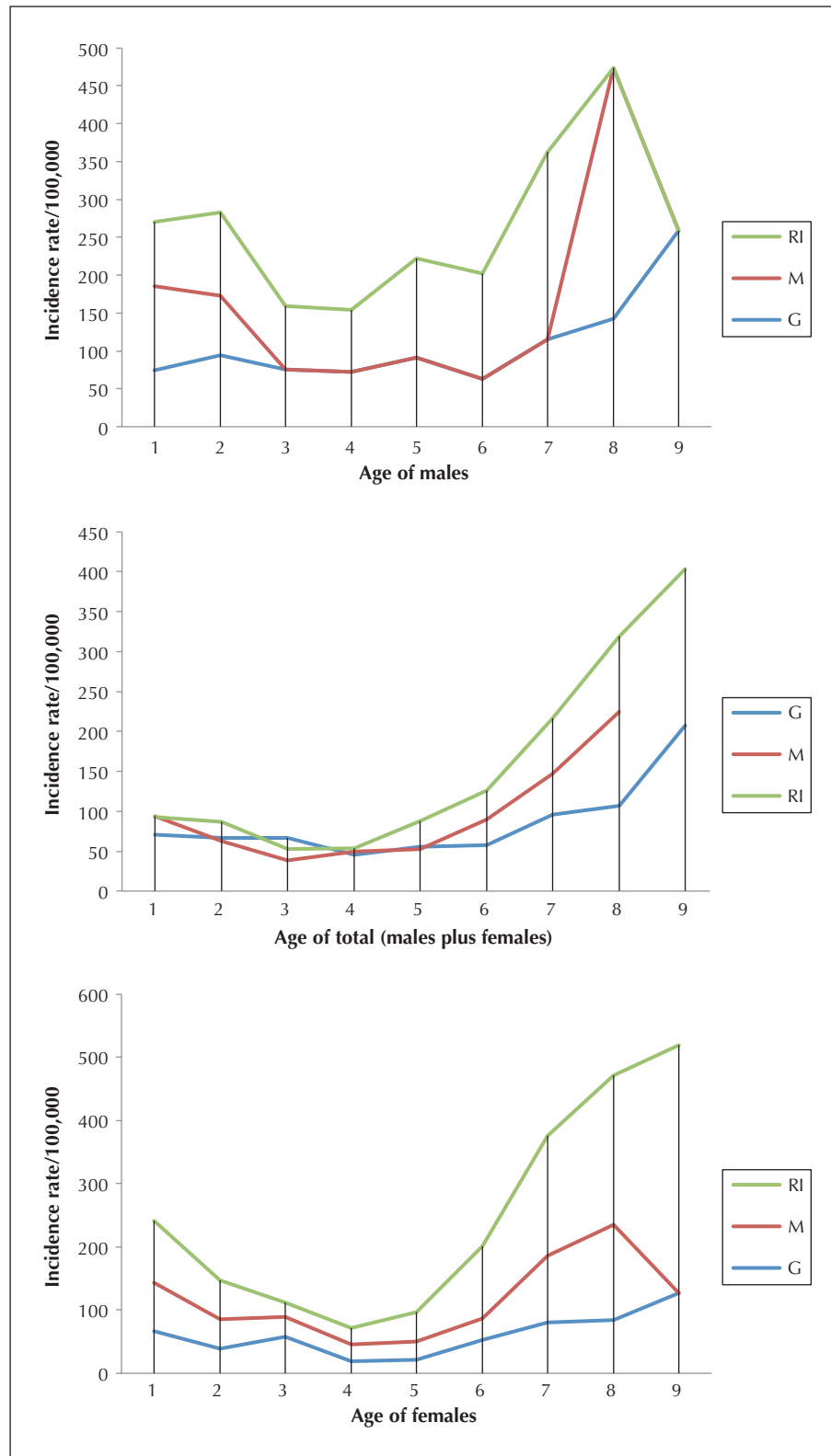


Figure 2. Age and gender-specific incidence of epileptic seizures.

1: <9 years age; 2: 10-19 years age; 3: 20-29 years age; 4: 30-39 years age; 5: 40-49 years age; 6: 50-59 years age; 7: 60-69 years age; 8: 70-79 years age; 9: >80 years age.

Table 3. Aetiological factors for provoked (PS) and unprovoked (UPS) seizures.

PS (%)	G	M	RI	G vs. M vs. RI	M vs. RI	Mainland vs. overseas
Trauma	2.0	18.7	11.1	0.001	0.12	0.0006
Stroke	18.5	20.6	10.4	0.09	0.02	0.5
Infection	6.2	4.7	x	0.97	x	0.2
Tumour	10.3	9.4	x	0.87	x	0.05
Post-operative	2.0	0	x	x	x	x
Toxic substances / drug abuse	20.6	11.1	x	0.11	x	0.00007
Alcohol withdrawal	29.8	30.1	27.4	0.88	0.66	0.88
Metabolic	6.1	4.8	x	0.97	x	0.2
Multiple factors	4.1	0	x	x	x	x
Unknown	0	0	51.1	0	x	x
Stable UPS (%)	G	M	R	G vs. M vs. RI	M vs. RI	Mainland vs. overseas
Trauma	11.6	5.4	5.4	0.11	0.8	0.06
Stroke	42	31.1	46.2	0.06	0.01	0.6
Infection	7.2	4.1		0.79		0.08
Perinatal factors	14.4	x	x	x	x	x
Alcohol	13	48.6	20.4	<0.0000	0.00001	0.0003
Encephalopathy	1.4	x	x	x	x	x
Malformation	8.6	5.4		0.83		0.06
Post-operative factors	1.4	x	x	x	x	x
Others	0	1.4		x		x
Unknown	0	4	28	<0.00001	0.00003	x
Progressive UPS (%)	G	M	R	G vs. M vs. RI	M vs. RI	Mainland vs. overseas
Tumour	29.6	29.4	30.4	0.99	0.9	0.9
Degenerative	14.8	11.6	21.7	0.59	0.5	0.8
HIV	37	52.9	17.3	0.04	0.01	0.9
Other infections	7.4	0	0	x	x	x
Metabolic factors	4	5.9	0	x	x	x
Autoimmune	7.4	0	0	x	x	
Unknown	0	0.2	30.4	0.0005	x	x
Unknown UPS (%)	G	M	R	G vs. M vs. RI	M vs. RI	Mainland vs. overseas
Cryptogenic	77.6	83.9	84.9	0.12	x	x
Idiopathic	22.5	16	15.1	0.12	x	x

G: Geneva; HIV: human immunodeficiency virus disease; M: Martinique; RI: Reunion Island; x: No information available or derived.
 *mainland indicates Geneva and overseas indicates Martinique and Reunion Island.

was statistically significant, while none of the aetiological factors were statistically significant upon comparison between overseas and mainland populations.

Unknown UPS

The incidence (per 100,000) of unknown UPS was greatest in the Reunion Island (44.2), followed by Martinique (40.4) and Geneva (20.8). The proportion of UPS was greatest in Martinique (50.2%), followed by the Reunion Island (44.0%) and Geneva (29.3%); $p=0.00001$. Aetiology was cryptogenic for 84.9, 83.9, and 77.6% in the Reunion Island, Martinique, and Geneva, respectively, and the rest were idiopathic. None of the differences were statistically significant ($p=0.12$ for each) (table 3).

Unclassified seizures

The proportion of cases with unclassified seizures was 0% in Geneva and Martinique and 1.4% in the Reunion Island.

Treatment

No treatment information was available from Martinique. More cases were treated after a first seizure in Geneva (59.0%) than in the Reunion Island (54.0%), mostly with monotherapy (92.2 and 83.4%, respectively). Polytherapy was used for 16.6% in the Reunion Island and 8.5% cases in Geneva.

Discussion

Only few studies have fully evaluated the incidence of seizures (provoked and unprovoked) using uniform methods and procedures (Forsgren, 1990; Loiseau et al., 1990; Hauser et al., 1993; Forsgren et al., 1996). We analysed data from three such studies that were conducted in three French-speaking populations: Geneva, Martinique, and the Reunion Island; the last two being overseas territories of France. The patients in these studies were recruited through different channels that included EEG labs. This was a particularly effective source in our studies, similar to what has been observed elsewhere (Loiseau et al., 1990). This method, however, depends upon two factors: availability of EEG labs in the population and the timely referral of patients to such labs. This may therefore not be an effective strategy for all populations, as noted in one European population where many of its cases were never referred to an EEG lab (Olafsson et al., 2005). In contrast, in Martinique, 77.0% cases were ascertained from EEG labs alone. In Geneva, all cases had had an EEG within, at the most, three months of recruit-

ment. In the Reunion Island, the exact number of cases sourced from EEG labs was not clear but 98.0% cases had had an EEG suggesting a high rate of patient referral to EEG labs in the Reunion Island.

Limited attention has been paid to PS, however, these are important since they manifest at a high frequency (18-35% in our populations) and are associated with a risk of mortality. PS may not self-limit and may culminate into epilepsy (Mauri-Llerda et al., 2000). Forty-percent (40.0%) of all first seizures are likely to be provoked (Beleza, 2012), however, there is variation between studies (Murthy and Yangala, 1999). Among our three populations, only Geneva had a frequency somewhat similar to this (36.0%). One possible reason for this could be the relative absence of hygiene-related infections in the overseas populations, which is the foremost risk factor for PS (Murthy and Yangala, 1999). In the overseas populations, these infections are now sporadically imported from neighbouring islands, particularly Haiti (Roman et al., 2000; D'Ortenzio et al., 2010). Interestingly, an earlier survey conducted in the Reunion Island had shown a very high frequency of such infections (Boyer-Vidal, 1972). This pleasing change indicates, on the one hand, that sanitation improvements may have reduced the occurrence of hygiene-related infections in the overseas populations, however, on the other hand, it may have paved a way for other important PS-related factors, such as trauma ($p=0.0006$), tumour ($p=0.05$), and use of toxic substances and drug abuse ($p=0.0007$), as noted in our analysis (refer to relevant sections above). Globally speaking, trauma, stroke, and toxic substance, alcohol, and drug abuse are among the commonest causes of PS (Mauri-Llerda et al., 2000). This is more so for populations where hygiene-related infections are less likely (Murthy and Yangala, 1999; Roman et al., 2000; D'Ortenzio et al., 2010). Many cases in the Reunion Island had unspecified aetiology (51.1%), thus a full comparison was not possible. In addition, the lowest incidence (per 100,000) of epilepsy in developed countries is 24.0 (Villaran et al., 2009), and, as noted in our analysis, the incidence of PS in Geneva was slightly higher (25.2) than this. This might suggest that in Geneva the risk of PS is greater than the risk of epilepsy. Similarly, in the overseas populations, the risk of epilepsy is likely to be higher than that of PS because the incidence of PS in the overseas populations was lower than the lowest incidence of epilepsy (24.0) reported in developed countries (Villaran et al., 2009).

UPS occur in the absence of precipitating factors and are caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures). They may be single or recurrent, however, our cohorts included cases with both single and multiple first UPS. The incidence (per 100,000)

of first UPS varies between 26 and 70.0. Estimates from other European and developed populations have shown different results, for instance in the Netherlands (55.0), USA (61.0) or Sweden (56.0) (Kotsopoulos *et al.*, 2005). The incidence of UPS varied between 45.6 and 81.2 and, in contrast to PS, was lowest in Geneva and highest in the Reunion Island. This is in agreement with our presumption that the risk for UPS and epilepsy is lower (as compared to PS) in Geneva and higher in the overseas populations. The foremost factor behind this risk differential (between mainland and overseas population) is alcoholism ($p=0.0003$) since this was about 2.5-fold more frequent in the overseas populations than in Geneva. Alcoholism is a major public health issue in the two overseas populations and, as an example, alcohol is particularly toxic in these populations with rum as the predominant type of alcohol consumed. About 17% of the general population show an addiction to alcohol in Martinique alone (Anger and Kintz, 2008). Stroke was a statistically significant aetiology in the Reunion Island and accounted for the risk differential (for stable UPS) when compared to Martinique ($p=0.01$). This is consistent with a high burden of stroke in the Reunion Island; much higher than in the French West-Indies (Martinique, Guadeloupe) (Chatot-Henry *et al.*, 2012). HIV was the only factor that could account for a higher risk of progressive UPS ($p=0.01$) in Martinique, as compared to the Reunion Island, while no factors were found to statistically differentiate risk for progressive UPS between Geneva and the two overseas populations. It is recognised that the incidence of HIV is high in Martinique (44/100,000) and even higher than in mainland France (33/100,000). Its proximity to Haiti, a high prevalence country, further augments seizure risk in Martinique. Prevalence of HIV is low and stable in the Reunion Island (Poubeau *et al.*, 2000). As summarised in table 2, PS and progressive UPS were twice as common in Geneva than elsewhere. It is difficult to draw authoritative conclusions as to why progressive UPS were more common in Geneva than elsewhere, although HIV is one of the possible causes of this difference (table 3). Similarly, the use of toxic substances and drugs, stroke, and tumour are possible causes for a population-to-population difference related to PS (table 3). A high proportion of unknown aetiology in the Reunion Island may also have contributed to a difference among populations.

The incidence of epileptic seizures (provoked and unprovoked) varied from 71.0 in Geneva to 80.6 in Martinique, and 100.4 in the Reunion Island. Characteristically, both overseas populations showed a higher incidence than in the mainland Caucasian population, which are ethnically mixed, diverse, and differ from other racial entities (e.g. Caucasians, Asians). It is well

recognised that those with diverse ethnic backgrounds have a much higher risk of epilepsy, epileptic seizures, and other neuropsychiatric disorders (Hesdorffer *et al.*, 2000; Amatić *et al.*, 2006; Theodore *et al.*, 2006). All cohorts demonstrated a two-peak distribution of overall seizure incidence, *i.e.* among very young and very old. This distribution is in agreement with classical bimodal distribution that is well recognised for populations that have well-developed healthcare infrastructure (Olafsson *et al.*, 2005), but is in contrast to non-industrialised populations where a single peak at early age followed by a sharp decline >60 years is observed (Mani *et al.*, 1998).

A conventional male to female seizure incidence ratio is considered to be 1.5:1 (Mignard *et al.*, 2009). This was consistent with the data from Geneva and the Reunion Island, but not Martinique where the incidence in males was nearly twofold that of females. This further supports our presumption about the leading role of male-related factors (alcoholism, HIV, and trauma) in this population (Smadja *et al.*, 2001; Anger and Kintz, 2008). Also, there was a male predominance among all age groups of all cohorts, except in the 0-9 age group in the Reunion Island (Mignard *et al.*, 2009) where there was a higher proportion of females than males. This could partially be due to the female preponderance of seizure transmission, as a result of complex genetic interactions (Dooze and Neubauer, 2001) that particularly manifest at an early age. Chikungunya in the Reunion Island (Sissoko *et al.*, 2009) and associated sequelae also show a female predominance (Padmakumar *et al.*, 2010) among those with neurological manifestations. Female predominance has also been noted in a few African populations as well (Goudsmit and van der Waals, 1983).

Given the higher male to female ratio of incidence of seizures in Martinique than elsewhere, one might suspect that the local socio-cultural factors may have influenced the reporting of seizures in females. There is little available information regarding the psychosocial aspects and the attitude of the people in Martinique or the Caribbean towards epilepsy. Thus, a possible role of local socio-cultural factors that may affect the disclosure of seizures or epilepsy may not be ascertained. However, because the population in Martinique has an effective and universal social security system and good healthcare access, we believe that the gender-specific difference in the incidence of seizures in Martinique is related more to risk factors than stigma or other socio-cultural factors.

Generalised seizures were most predominant (63.8%) in Martinique and least predominant in the Reunion Island (48.8%). There is no single or straightforward explanation for this and this difference could be partially due to the complex difference in the distribution

of various aetiologies (Misra and Kalita, 2011) and partially due to demographic differences, for instance, seizures in older subjects tend to generalise less often than in younger subjects (Luhdorf et al., 1986). A relatively lower frequency of generalised seizures in the Reunion Island could also be due to the high frequency of unclassified and undetermined seizures in this population (19.3%), relative to other populations. The difference in the frequency of different seizure types between our populations could also be due to the under-reporting of partial seizures, which are often less likely to be detected, and this could be a limitation of this study or other similar studies. This type of relatively “non-visible” seizure can be more effectively detected through other methods of case ascertainment, such as door-to-door visits. This is because someone with “visible” seizures (*i.e.* generalised or violent seizures) would have sought healthcare differently to someone with minor, infrequent seizures or seizures that can be easily overlooked by the patients themselves.

Theoretically, first seizures are not treated, however, currently, there are no clear guidelines. Some studies advocate that an early treatment does not affect prognosis beyond two years (Massimo et al., 1997; Marson et al., 2005; Leone et al., 2006; Seneviratne, 2009; Leone et al., 2011), while other studies have shown a high seizure-recurrence risk even among low-risk subjects, necessitating early intervention (Ramsay, 2005). An early intervention reduces the absolute risk of seizure recurrence by 51% (Seneviratne, 2009). In our cohorts, up to 59.0% cases were being treated after their first seizure, especially in Geneva, indicating that current practice is such that not all cases are treated. Polytherapy was nearly double in the Reunion Island compared to Geneva (16.6% vs. 8.5%) and may indicate the presence of high risk parameters in this population, such as severe seizures, status epilepticus, or other parameters of high risk. Another survey in the Reunion Island estimated an incidence of 8.5/100,000 of newly-diagnosed, first-ever-onset status epilepticus (personal data). Interestingly, two population-based prospective studies from Switzerland yielded distinct results, for example, a standardised annual incidence of 10.3/100,000 in a French-speaking part of Switzerland (Coeytaux et al., 2000) and an incidence of 15.5/100,000 in Geneva (Jallon et al., 1999b). These two estimates (Jallon et al., 1999b; Coeytaux et al., 2000), along with our own from Geneva and the Reunion Island, are lower relative to studies from other populations such as in the US (DeLorenzo et al., 1996). This difference can, in part, be explained by restricted inclusion criteria such as non-inclusion of patients with anoxic encephalopathies (highly fatal outcome) or due to the possibility that those with repetitive seizures may have been managed in pre-hospital care. However, the case

fatality rates in Europeans are lower than in other populations (DeLorenzo et al., 1996).

Our data represents more of a population-based than EEG lab-based study, even though a large number of cases were sourced from EEG labs for all of our study populations. As mentioned in *table 1*, several other sources of recruitment, other than EEG labs, were used, both public and private, as was practically feasible in a given population. As an example, 260 general practitioners were recruited to refer cases from Martinique and eight private neurologists were recruited from Geneva. Despite this, we can still expect that some cases were not included in our cohorts.

Conclusion

Overseas populations that are ethnically diverse showed higher overall incidence of seizures (PS and UPS) than a Caucasian mainland population. The same was noted for incidence of UPS and stable UPS. Geneva has a higher risk of PS than the overseas populations, which is most likely due to tumour and use of toxic substances and drug abuse. The risk of UPS in Geneva is most likely due to trauma and hygiene-related infections. For Martinique, alcoholism and HIV are the foremost factors associated with PS and UPS, while stroke is an important aetiology in both Martinique (PS) and the Reunion Island (UPS). Relative eradication of hygiene-related infections in the overseas populations may have paved a way for the emergence of other significant aetiologies in the tropical overseas populations. Epileptic seizures demonstrated bimodal distribution and male predominance, especially in Martinique, where males have a greater seizure risk, compared to other populations, signifying, in particular, the importance of alcoholism and HIV in this population. Evidence-based guidelines on whether or not the first seizure should be treated in these populations should be delineated in the light of our results. The public agencies of these populations should lay down strong mechanisms in order to prevent (or control) many of the seizure-related risk factors. □

Disclosures.

None of the authors have any conflict of interest to disclose. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed equally in the preparation of the manuscript. The material in the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This work has not been presented in any meeting.

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