Neuropsychiatric Problems in 2,500 Long-Term Young Travelers to the Tropics

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Background: The prevalence and features of travel associated neuropsychiatric problems (NPP) and their relation to previous psychological consultations, antimalarials and recreational drug use have not been adequately studied.

Methods: A two-phase postal and telephone survey has been conducted among 2,500 young travelers to tropical countries. We measured the rate and duration of NPP, characterized their features, and their association with previous psychological profiles, itinerary, type of travel, consumption of recreational drugs, and malaria prophylaxis.

Results: First phase: Out of 1,340 respondents, 151 (11.3%) indicated that they had NPP during travel, in contrast with 2.3% who needed psychological consultation before travel (p<.001). Second phase: 117 of 151 responded to the study questionnaire. The mean age of the respondents was 24.4 years, 54.7% were female, and the mean stay abroad was 5.3 months. The most common NPP were sleeping disturbances (52.1%), fatigue (48.7%) and dizziness (39.3%). Thirty-three travelers (2.5%) had severe symptoms, and 16 (1.2%) had symptoms lasting more than 2 months. Seven travelers had pure or mixed depressive symptoms. Consumption of recreational drugs was admitted by 22.2%. Mefloquine was used significantly more often by those who suffered NPP, than by the entire cohort (98.2% vs. 70.7%; p<.001).

Conclusions: Long-term travel to the tropics was associated, in this cohort, with a considerable rate of neuropsychiatric symptoms. The majority of the responding travelers were females, used mefloquine as prophylaxis, and at least one fifth used recreational drugs.

International travel is growing every year.[1] The World Tourism Organization estimates there were 595 million international tourist arrivals in 1996.[2] Travel, especially long-term travel, across borders and cultures may be psychologically demanding.[3,4]

Psychiatric and neurologic problems during travel may stem from four major sources: previous personality traits, stressful events during travel, illicit drug abuse, and side effects of antimalarials or other drugs. The current Israeli recommendations for malaria prophylaxis have been changed and call for the use of mefloquine in all areas with resistant *P. falciparum*.[5] If an association exists between the use of antimalarials and the development of neuropsychiatric problems (NPP), this recommendation may influence the prevalence of NPP.

The scope and characteristics of these NPP have not been studied on a large cohort of travelers. We studied the prevalence and features of neuropsychiatric problems (NPP) in a cohort of 2,500 young Israeli travelers to the tropics, and the association of these NPP with the use of antimalarials and recreational drugs.

Methods

The travel clinic at the Bnai Zion Medical Center provides service to approximately 1,300 travelers per year, who self-refer to the clinic. Services are paid out of pocket. The clinic has been operating since February 1992.

Each traveler is requested to fill out a questionnaire including demographic, itinerary and vaccination data, which are stored on a computerized database. Prior to vaccination the travelers attend a 40-minute lecture covering three major topics: diarrheal diseases, malaria prophylaxis, and available vaccinations. Vaccination and advice to travelers are given according to the Israeli Health Ministry and the most recent Centers for Disease Control and Prevention (CDC) recommendations for travelers, which are updated weekly via the Internet.

Since October 1993, an abbreviated psychological profile paragraph has been incorporated into the pre-

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vaccination questionnaires. Answering this part of the questionnaire is not mandatory. We identified all travelers who have been advised at our clinic between January 1994 and June 1996.

Phase I

Two thousand five hundred travelers seen during this period were sent an introductory letter that described the purpose of our study, and included two questions: "Have you suffered during, or soon after your trip, from neurologic or psychiatric symptoms such as dizziness, numbness, nightmares, or depression?" and "Have you taken malaria prophylaxis and if so what type?" A stamped return-envelope was included with every letter.

Phase II

All those who responded positively to the first question were sent a second, more detailed questionnaire. In light of the delicacy (intrusiveness) of psychological questionnaires, we aimed at gathering maximum information with a minimum of questions. The questions related to: dizziness, sleep disturbances, vivid dreams, numbness (tingling), dyspnea, palpitations, weight loss, nausea, fatigue, hot-cold spells. The latter six items were counted only if they appeared together with one of the other parameters. Other questions were restlessness, lack of mood, inability to function, loss of confidence and inability to concentrate (attention deficit). A final (yes/no) question related to the consumption of illicit drugs such as marijuana, hashish, "ecstasy," "speed," "trip," or mushrooms. No answer (either yes or no) to this question was considered as probably positive.

For each existing symptom the traveler was asked to categorize the length of time that the symptom had lasted (either during or extending to the posttravel period). Four grades of time lengths were available: 1–less than 1 week, 2–less than 1 month, 3–less than 2 months, and 4–more than 2 months. Those who had one or two symptoms lasting less than 1 week were categorized as "mild" cases, those who had at least two symptoms lasting more than 2 months were categorized as "severe."

Nonrespondents were sent a second questionnaire, and if still not responding were contacted by telephone.

The data were entered on an excel sheet. Additional data was extracted from the pretravel forms: age, destination, traveling alone/with companion, future plans, military profile, need for mental health aid during service, and attraction to meditation/cults. Categorization of mental illnesses followed the guidelines of the Diagnostic and Statistical Manual of Mental Disorders IV manual.[6] All the data were analyzed by the Software Package for the Social Sciences (SPSS) 7.0 software.[7]

Results

One thousand three-hundred and forty of the 2,500 travelers (53.6%) responded to the phase I questionnaire. One hundred fifty-one (11.3%) of them indicated that they had some kind of neuropsychiatric symptom. Despite the repeat mailings and attempts to reach respondents by telephone, valid responses to phase II questionnaires were obtained from 117 responders (77.5%).

Sixty-four (54.7%) of the respondents were female, a rate which is significantly ($p<.001$) higher than their respective percentage (38%) among outgoing travelers. The mean age of the group was 24.4 ± 6.8 years (median = 22; range: 18-64 years). The majority of travelers (n=87; 74.3%) headed for Southeast Asia (Thailand, Nepal, India), 20 (17.1%) for South America, 8 (6.8%) for Africa; for two travelers the destination could not be ascertained. The length of stay abroad ranged from 0.5–24 months, with a mean of 5.3 ($\pm$ 3.4; 95% confidence limits: 4.7-6.1) months, and equivalent to 620 person-years.

Malaria prophylaxis was taken by 1,016 (75.8%) of the travelers who responded to the first letter. Mefloquine was taken by 948 travelers (70.7% of respondents) and 68 (5%) took chloroquine alone, or combined with proguanil; twenty-four percent of our travelers did not take any prophylaxis. Twenty-six of the 117 travelers (22.2%) indicated that they had consumed recreational drugs, while 77 (65.8%) denied doing so. An additional group of 14 travelers (12.0%) did not mark this question and were thus considered probable consumers.

The most commonly encountered symptoms (Table 1) were sleeping disturbances (52.1%), fatigue (48.7%), and vivid dreams (47.9%). Twenty travelers had at least one symptom, which lasted for more than 2 months (see Table 1). Most of those with "long duration symptoms" suffered from fatigue, or lack of mood. Mefloquine was used significantly more often by those who suffered NPP, than by the entire cohort 115/117 vs 948/1340 ($p<.001$, Pearson's χ^2).

We tried to identify those travelers whose symptoms could not be attributed to drug abuse (Table 2). Only those travelers who had had at least two symptoms during the time period were included in this tabulation. Twenty travelers had at least two symptoms for more than 1 week, but only 13 of them stated they had not used drugs; sixteen travelers had symptoms for more than 2 months and 9 of them (7.7% of 117 or 0.7% of total respondents) stated they had not used drugs. The latter group of 9 travelers was analyzed by the DSM IV criteria: one patient had pure neurological symptoms (dizziness + numbness), two fulfilled the criteria for major depression and two fulfilled the criteria for a mixed anxiety-depressive disorder. Three travelers

Table 1 Frequency and Duration of Neuropsychiatric Symptoms among 117 Travelers to the Tropics

Symptom	*Frequency of Positives*	*%*	*Duration*		*NPP Lasting >2 Months (n)*
			Mean	*Median*	
Sleep disturbances	61 vc=111	52.1	1.8 vc=56	1.0	10
Fatigue	57 vc=110	48.7	1.9 vc=51	1.0	
Vivid dreams	56 vc=108	47.9	1.7 vc=48	1.0	6
Lack of mood	47 vc=110	40.2	2.0 vc=42	2.0	11
Dizziness	46 vc=109	39.3	1.6 vc=40	1.0	6
Nausea-vomiting	42 vc=108	35.9	1.3 vc=36	1.0	
Inability to function	33 vc=109	28.2	2.1 vc=26	2.0	5
Restlessness	33 vc=108	28.2	2.0 vc=28	1.0	7
Weight loss	26 vc=108	22.2	2.2 vc=36	2.0	
Attention deficit	25 vc=105	21.4	2.7 vc=22	3.0	8
Loss of confidence	24 vc=109	20.5	2.3 vc=21	2.0	6
Palpitations	23 vc=109	19.7	2.1 vc=21	2.0	
Dyspnea	21 vc=108	17.9	2.3 vc=18	2.0	
Numbness	15 vc=107	12.8	1.7 vc=15	1.0	3
Heat-cold waves	14 vc=105	12.0	1.8 vc=14	1.0	

vc = valid counts (number of travelers filling this item).
NPP = neuropsychiatric problems.

had depressive symptoms not fulfilling DSM IV, and one had panic attacks.

Two of the 117 responding travelers indicated in their pretravel questionnaires that they had an interaction with a psychologist, and two others were attracted to meditation/parapsychology. All four of these travelers have used mefloquine, but only one had severe symptoms that lasted more than 2 months (without taking recreational drugs).

Discussion

This study found that 11.3% of young Israeli travelers to the tropics suffered neuropsychiatric symptoms. Thirty-three travelers out of 1340 respondents (2.5%) had severe symptoms, which prevented them from functioning normally, and 16 travelers (1.2%) reported prolonged symptoms, which lasted more than 2 months.

Psychiatric problems in travelers appear to exert a nonnegligible burden on both the traveler and society. Sauteraud and Hajjar found that 15-20% of evacuations of French citizens from tropical countries were due to mental problems.[4] A Medline search revealed only scant reports that studied neuropsychiatric symptoms in travelers systematically.[3,8,9] The groups studied included older travelers,[3] or those evacuated on an emergency basis for political reasons.[9] The impact of antimalarials in this context was not evaluated in detail. Mefloquine, which was introduced into the world market 10 years ago, gained worldwide popularity as malaria prophylaxis, because of the growing number of falciparum resistant strains and the ease of administration. Since its inception the manufacturer has warned users of the possibility of neuropsychiatric side effects,[10] which were estimated to occur at a rate of 1/100,000 users. Recent reports indicate that the rate may be considerably higher, more in the range of 1-27%.[11–14]

Our interest in this research followed a request for help by five travelers who had returned from a trip to the tropics. These travelers, who were all in their early twenties, presented with a variety of symptoms ranging from nightmares to frank depression.

Our typical travelers are 20-25 years old who have just finished 2-3 years' compulsory military service. As such, most of them were healthy, with a flawless military profile score of 97. It was therefore somewhat surprising that 11.3% responded positively to the first questionnaire. This rate is significantly higher ($p<.001$) than the 2.3% who indicated in the pretravel questionnaires that they had some kind of interaction with a mental health officer during their military service.

Table 2 Neuropsychiatric Symptoms and Recreational Drug Use in Travelers with Long-Duration Complaints

*Time Parameter**	*No.*	*Definite Drug Users*	*Probable Drug Users*	*No Apparent Cause for Sx*
2 or 3	20	4	3	13
4	16	4	3	9

* = Time parameter 2 indicates symptoms lasting less than 1 month; 3 indicates symptoms lasting less than 2 months; 4 indicates symptoms lasting more than 2 months.
Probable drug user = Did not mark this item in the questionnaire.
Sx = Symptoms.
Only travelers who had at least two symptoms for the indicated time period were included in this table.

However, both of these figures are considerably lower than the reported rate of mental disorders in young Israeli adults.[15] According to this large cohort study the 6-month prevalence rate of mental disorders have reached a staggering figure of 19% at the definitive level. Generalized anxiety (3.5%) and major depressive disorders (3.0%) top the list. These discrepancies between our results and this study raise the query whether a community based cohort is the appropriate control for travelers, or should we rely on internal controls among travelers. It can be argued, for example, that people with major anxiety or depressive symptoms would not embark on a journey to tropical countries. In addition to these reservations we believe that results of postal surveys should always be taken cautiously in light of a possible recall bias.[16] It cannot be excluded that recall bias may have caused an underestimation of the number of positive responders, but on the other hand may have overestimated the rate of those complaining of severe symptoms.

We found a significantly higher rate of females among the respondents. Other researchers have noted similar findings. Phillips and Kass[17] have noted that females consistently reported more adverse effects than males, and were more likely to discontinue mefloquine because of adverse effects. These authors also point out that over-reporting by females is unlikely to explain why they suffered the most severe adverse effects. Similarly, in a large German study, females taking mefloquine have reported significantly more side effects than males.[18] The same trend was also seen in the study by Barrett et al.[19] where 8/10 patients with disabling neuropsychiatric adverse events with mefloquine were females.

The use of recreational drugs may have a major impact on NPP. Twenty-six of the 117 respondents (22.2%) to the second questionnaire admitted using recreational drugs. We speculate, however, that this represents a minimum figure as 14 additional travelers failed to mark this item on their questionnaires. Although these alarming figures cannot be extrapolated to the entire cohort they serve as a reminder to us that further work should be carried out to minimize this phenomenon. Alcohol drinking has been anecdotally linked to mefloquine adverse effects.[20]

Since a recent report[15] has shown that the rate of alcohol consumption among Israeli youngsters is extremely low (0.5%) we refrained from including this parameter in the second phase questionnaires.

The reasons for the flow of Israelis to the tropics are as diverse as the different natures of the travelers themselves. Most youngsters believe that these trips may serve as psychological catharsis following three years of demanding military service. In fact, for lengthy periods abroad they are under stress. At the outset this stress may arise from adjustment to different time zones,[8] languages and local culture while later the disconnection from home, fear from diseases and monetary constraints will play a greater role. The lack of rules, the mystic atmosphere and the temptation to use illicit drugs may all serve as co-stressors. A minority of the travelers, especially youngsters, may require psychiatric hospitalization. Based on data provided by the Israeli consulate in Bangkok, during the period July 1994 - October 1996, 49 Israelis required hospitalization in Thailand for psychiatric reasons, and 26 of them needed to be transported home urgently (personal communication: Offer Mazar, Israeli consul to Bangkok). Some of those returning home required prolonged hospitalization in mental health institutions for acute psychotic states or major depression.

Although formal psychiatric testing has not been carried out, eight patients of the studied cohort apparently had psychiatric disorders; four of them had well substantiated pure or mixed depression according to the DSM IV.[6] The diagnosis of depression by the DSM IV guidelines is dependent on two important criteria: that the symptoms have been present for at least 2 weeks and that they represent a clear change from previous functioning. We adhered to these criteria in reaching the diagnosis.

It is noteworthy that symptoms in some travelers failed to wane for months after repatriation. As none of these travelers had an underlying NPP, it may be theorized that we are facing mefloquine-associated late effects. Pharmacokinetic and pharmacodynamic properties of mefloquine may indeed explain the drug's association with neuropsychiatric disorders, the great inter-individual variability, and the possibility of a prolonged effect after the drug was stopped. Firstly, the chemical structure of mefloquine resembles that of quinine,[21] which has well documented effects on neuroexcitable membranes in the central nervous system. Secondly, mefloquine, a lipid soluble molecule, penetrates well through the blood-brain-barrier.[22] This fact is in agreement with the finding that neuropsychiatric adverse reactions to mefloquine do not necessarily correlate with the drug's serum concentration.[23] Thirdly, mefloquine has an extremely long serum elimination half-life of up to 21 days,[21] which may explain the long duration symptoms of some of our travelers. Fourthly, there is a great inter-individual variability, including ethnic and gender[24] related differences in mefloquine's absorption, metabolism, and central nervous system (CNS) distribution. Indeed, gender related differences were also found in the present study. Pharmacokinetic studies on patients suffering neuropsychiatric symptoms, while on mefloquine, are needed in order to fine tune the recommendations of mefloquine prophylaxis.

One should exercise caution in determining the etiology of anxiety or major depression since they may stem from psychosocial, genetic, or biological factors. Since the pretravel questionnaires in the eight patients who had severe symptoms failed to reveal psychosocial problems, and illicit drug abuse was denied, it is conceivable that this derangement was induced by mefloquine. Furthermore, our logistic regression model failed to reveal a significant association between neuropsychiatric symptoms and either travel destination, illicit drug abuse, travel alone, or previous encounter with a mental health officer. This finding underscores the role of mefloquine in these symptoms.

This study has certain limitations. First, a psychological study is intrusive by nature. Bearing in mind that this was mostly a postal, and not an interview type survey, we could not employ very detailed questionnaires like the SCL-90, or MMPI.[25] Even with our limited structured questionnaire the response rate reached 77.5%. Second, we could not rule out the influence of the media on the respondents. Some of our travelers have probably heard about the potential side effects of mefloquine from media publications.

Conclusion

Long-term travel of youngsters to the tropics is associated with more than just a negligible rate of neuropsychiatric symptoms. These symptoms may partly stem from baseline personality traits, illicit drug abuse, and/or may be mefloquine related. As mefloquine is still considered the most effective chemoprophylactic agent available, we believe that careful screening of potential mefloquine users may reduce the incidence of NPP. Future studies employing formal neuropsychiatric testing should be carried out to substantiate our findings and explore avenues to minimize these symptoms.

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