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The impact of SARS on epilepsy: The experience of drug withdrawal in epileptic patients

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Summary

Background: During the 2003 severe acute respiratory syndrome (SARS) outbreak, many patients avoided hospital visit because of fear of infection. Antiepileptic drug (AED) withdrawal is a risk factor for seizure recurrence. Therefore, seizure control during the SARS outbreak is a good model for examining the impact of drug withdrawal in seizure control.
Methods: All seizures experienced by each patient before, during, and after the SARS outbreak periods were registered in each patient's seizure diary. The patients were divided into four groups according to the presence of drug withdrawal as well as seizure attack. In each group, seizures occurring during three different periods were compared. Risk factors for seizure recurrence were also examined.
Results: Of 227 cases, 49 stopped taking medication during the outbreak. Among them, 28 suffered seizure attacks during AED withdrawal. Four cases developed cluster attacks and two cases had status epilepticus after AED withdrawal. AED withdrawal produced a significant increase in seizure frequency. The major risk factors for withdrawal seizures were symptomatic etiologies, polytherapy and non-seizure free before AED withdrawal.
Conclusions: The SARS outbreak adversely affected seizure control because of AED withdrawal. Patients with polytherapy, non-seizure free and symptomatic etiologies were more susceptible to recurrence of seizures after AED withdrawal.

Introduction

According to the World Health Organization, a total of 8477 people world wide were infected with severe acute respiratory syndrome (SARS) during the February to July 2003. Of these, 813 died. During

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this outbreak, a total of 664 probable cases of SARS were reported to the Taiwan Center of Disease Control. Among them, 71 died. On February 21, the first identified SARS patient in Taiwan returned from travel to China. Beginning in mid-April, unrecognized cases of SARS led to a large nosocomial cluster and subsequent SARS-associated coronavirus transmission to health-care facilities and community settings.[1]

On April 24, the Taiwan Department of Health directed the first phase of containment: hospital shutdown in one large municipal hospital in Taipei; another private hospital in Taipei was shut down 5 days later.[1] A patient, who visited the second Taipei hospital to be shut down moved from Taipei to Kaohsiung in late April and was admitted to our Kaohsiung Chang-Gung Memorial Hospital for renal stone. Unfortunately, she previously had been infected with SARS at the Taipei hospital and the virus was undiagnosed in our ward for 2 days. The delay of diagnosis led to a large nosocomial cluster of SARS in our hospital. The hospital closed all clinics including the emergency department, for 18 days, and visitors were barred. Yellow police tape barricaded all but one entrance to the hospital.

Medical staffs were infected during the outbreak, and some died. The public began to avoid visits to the doctors, nurses, pharmacies and hospitals. The panic became so widespread that some the doctors were shunned by neighbors when they returned to their homes.

When nature disasters occurred, the government and health care delivery system can quickly respond to request for help. Regarding chronic diseases, natural catastrophes still increase morbidity rates for hypertension, arrhythmia, acute myocardial infarction, and diabetes.[2,3]

The SARS outbreak was a difference experience. Patients were afraid to visit hospitals, pharmacies, and private clinics. Many patients even chose to stop taking drugs. Noncompliance became a major issue in the management of chronic diseases. Suddenly stopping medication may have a huge impact on the treatment of many diseases. For example, uncontrolled seizures are a major risk factor of mortality in epilepsy.[4,5] Sudden withdrawal of antiepileptic drug (AED) is a risk factor for seizures,[6] even status epilepticus.[7] Irregular anticonvulsant consumption is worse than no therapy at all because of withdrawal seizures[8] or even sudden unexpected death.[9,10] Thus, seizure control in epileptic patients is a good example of the consequences of the SARS outbreak.

The aim of this study was to determine whether drug withdrawal was a precipitating factor for seizures, status epilepticus or even sudden unexpected death during the SARS outbreak period. We further examined the risk factors for drug withdrawal induced seizures.

Methods

During the SARS outbreak period, our hospital closed all out-patient clinic (OPDs) from May 16 to June 2, 2003. Although doctors tried to contact registered patients, interview them by telephone, and mail them their medications, many patients could not be reached due to outdated or incorrect contact information. After the SARS outbreak, the subjects of the study and their families were interviewed regarding their epileptic attacks before, during, and after the SARS outbreak, specifically recording the type and frequency of seizures, any withdrawal of medication, sleep habits and other factors associated with seizures.

All of these epilepsy patients had undergone neurological examinations, monitoring of antiepileptic medications, electroencephalography (EEG), and computed tomography (CT) or magnetic resonance image (MRI) of the brain. Classification of their seizures was based on their history and the above diagnostic tools according to the 1981 classification of epileptic seizures from the International League against Epilepsy.

In our epileptic clinic, around 300 epileptic cases were regularly followed up in monthly basis. They were all recruited into the study. All seizures that occurred before, during, and after the SARS outbreak period were registered in the patient's medical history, seizure diary or both. With the help of such a diary, a patient keeps a personal annual registration of seizures. Unfortunately, 44 of the 271 patients did not keep seizure diaries regularly and could not be included in the analysis of seizure frequency. Although 10 self-report seizure free patients of these 44 cases stopped the drug in the SARS period, and 3 among them had seizure relapse in drug-withdrawal period. They were still excluded because of possible non-reliable seizure-free history. Nineteen new cases were also excluded because their history of seizures did not extend to 6 months prior to SARS outbreak. No cases of sudden death were reported during the SARS period.

The definition of ''before SARS outbreak'' is the period before our hospital closed and when patients still had access to medication; ''during SARS outbreak'' is the period when the hospital was closed or until the patient resumed medication after drug withdrawal; ''after SARS outbreak'' is the period after the SARS outbreak when the patients began to visit the OPD and undergo follow up observation for 6 months.

Table 1 Demographic characteristics of the patients.

	Stop drug/attack	Stop drug/no attack	Continue drug/attack	Continue drug/no attack	Total
Patient number	28	21	53	125	227
Seizure etiology					
Idiopathic	7 (25%)	17 (81%)	8 (15%)	51 (41%)	83
Symptomatic	21 (75%)	4 (19%)	45 (85%)	74 (59%)	144
Seizure type					
Generalized	5 (18%)	11 (52%)	4 (8%)	33 (26%)	53
Partial	23 (82%)	10 (48%)	49 (92%)	92 (74%)	174
Treatment					
Monotherapy	12 (43%)	16 (76%)	11 (21%)	62 (49%)	101
Multiple drugs	16 (57%)	5 (24%)	42 (79%)	63 (51%)	126
Six months before SARS					
Seizure free	20 (71%)	21(100%)	2 (4%)	117 (94%)	160
Non-free	8 (29%)	0	51 (96%)	8 (6%)	67
Six months after SARS					
Seizure free	17 (61%)	19 (90%)	10 (19%)	110 (88%)	156
Non-free	11 (39%)	2 (10%)	43 (81%)	15 (12%)	71

According to drug withdrawal and number of seizure attacks during the SARS period, the patients were divided into the following four groups for comparison of the impact of SARS on seizure control: (1) ''stop drug/attack'', (2) ''stop drug/no attack'', (3) ''continue drug/attack'', and (4) ''continue drug/no attack''. In each group, seizure etiology, seizure type, therapy, and seizure control were listed for the comparison in different group.

Seizure frequency ''before SARS period'' is the average numbers of seizures per month during the 6 months prior to the SARS outbreak; seizure frequency ''during SARS period'' is the number of seizures during the outbreak; seizure frequency ''after SARS period'' is the average number of seizures during the 6 months after the outbreak.

The age range of the remaining 227 cases was 9—93 years, mean 37.3 ± 14.8 years. One hundred and fifteen were males; 53 had primary generalized seizures and 132 had secondarily generalized tonic—clonic seizures; 31 had complex partial seizures and 11 had simple partial seizures. One hundred and one patients were on monotherapy; 93 were on two drugs, 28 were on three drugs, and 5 were on four drugs. To compare the risk factors for seizure recurrence, primary generalized seizure was classified as generalized. Simple partial, complex partial, and secondarily generalized seizures were classified as partial. Those using only one type of drug were classified as monotherapy; the others were classified as polytherapy. As for the etiologies, those with central nervous system (CNS) infection, tumor, stroke, vascular anomaly, traumatic hemorrhage, and developmental disorders were classified as symptomatic. No etiologies were found in the idiopathic group.

According to drug withdrawal and number of seizure attacks during the SARS period, the patients were divided into the following four groups for comparison of the impact of SARS on seizure control: (1) ''continue drug/no attack'', (2) ''continue drug/attack'', (3) ''stop drug/no attack'', and (4) ''stop drug/attack''.

The seizure frequencies were analyzed by using nonparametric Wilcoxon tests for each group during the before-SARS outbreak in comparison to the SARS outbreak and during the SARS outbreak in comparison to the after SARS outbreak. Chi-square tests were used for comparing the differences between the ''stop drug/no attack'' and ''stop drug/attack'' groups regarding seizure etiology, seizure type, and number of different drugs. Logistic regression was used to analyze the risk factors for seizure recurrence, including age, sex, drug withdrawal, seizure etiology, seizure types, and number of different drug types used.

Results

During the SARS outbreak, 49 of 227 cases did not receive medication due to loss of contact with medical care providers. Among these cases, 28 cases suffered seizure attacks during the outbreak. Among them, four cases received emergency room (ER) treatment because of cluster attacks. Two other cases were admitted to Intensive Care Unit (ICU) because of status epilepticus. Twenty cases, including four sent to ER and two sent to ICU, were seizure free for at least 6 months before SARS outbreak. Another eight cases had seizures before the SARS outbreak period, but the acute withdrawal of drugs also produced a significant increase in the number of

seizures compared to the previous period. After SARS, the 28 cases returned to the OPD, and the drugs were reinstituted; seizure frequency then showed a marked decrease during 6 months observation period ($P < 0.001$) (Fig. 1). Seventeen of the 28 cases were seizure free for 6 months. The seizure types were 5 generalized, 10 secondarily generalized, 8 complex partial seizures, and 5 simple partial seizures. The etiologies for the seizures were 7 idiopathic and 21 symptomatic including tumor, mesial temporal sclerosis, stroke, and developmental disorders. Twelve cases received monotherapy, and the other 16 cases had at least two drugs for seizure control (Table 1).

Twenty-one of 227 cases did not have drugs but they did not have seizures after drug withdrawal. All were seizure free during the previous 6 months. Eleven cases were generalized seizures and ten cases were secondarily generalized seizures. The etiologies for the seizures were 17 idiopathic, 1 stroke. Sixteen cases received monotherapy, other five on polytherapy. After the outbreak, they kept drug-free after the consultation. Nineteen cases remained seizure free at the 6 months follow up after the SARS outbreak. Another two had recurrent seizures and they received treatment again.

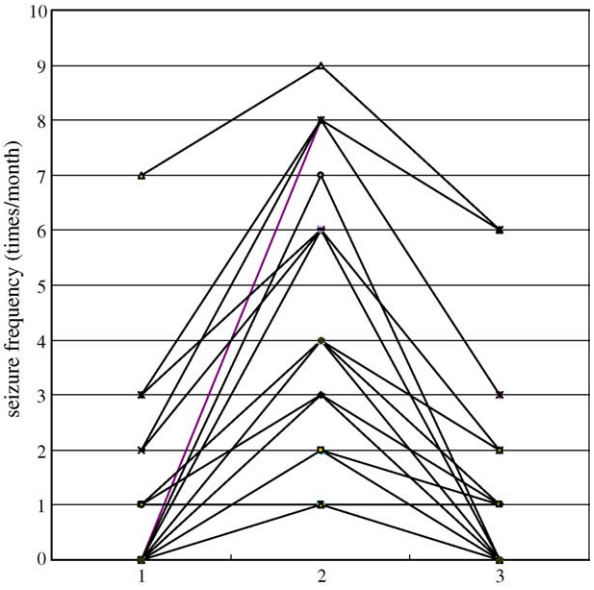

Figure 1 Seizure frequency changes in the group of ''no drug/attack''. On *X*-axis: (1) half year period before SARS outbreak; (2) the period during the SARS outbreak; (3) half year period after SARS outbreak. *Y*-axis represent the seizure frequency as times per month. Twenty cases were seizure free in period 1, they had seizures ranged from one to seven times in period 2 and the seizures were controlled in period 3. Eight cases had one to seven seizures in period 1, they also showed frequency increase in period 2 and seizure reduction in period 3. The difference of periods 1—3 was significant ($P < 0.001$).

In the above two groups, seizure type ($P = 0.01$, χ^2-test), etiology ($P = 0.001$), number of drugs ($P = 0.019$), and seizure free before SARS ($P = 0.007$) were significantly different. Partial seizure, symptomatic etiology, polytherapy, and still seizure attack before SARS were more common in the ''stop drug/attack'' group.

One hundred and twenty-five cases had drugs and were seizure-free during the SARS outbreak period. In the previous 6 months, 117 of these cases were seizure-free for 6 months. Statistical analysis shows seizure frequency decreased during SARS period ($P = 0.05$). The seizure types in this group were 33 generalized, 12 complex partial, 2 partial, and 78 secondary generalized seizures. The etiologies for seizures in this group were 53 idiopathic or cryptogenic and 72 symptomatic. Sixty-two cases received monotherapy, 49 cases received two drugs, 13 received three and 1 received four drugs.

Fifty-three cases had drugs but still suffered seizure attacks during the SARS period. In this group, only two cases were seizure-free in the previous 6 months. According to statistical analysis, seizure frequency did not increase during the SARS period ($P = 0.863$). The seizure types in this group were 4 generalized, 11 complex partial, 4 simple partial, and 34 secondarily generalized seizures. The etiologies for seizures in this group were 8 idiopathic, and 45 symptomatic. Eleven cases have treated with monotherapy, 23 with two drugs, 15 with three drugs, and 4 with four drugs.

In the above two groups, seizure type ($P < 0.0000$), etiology ($P < 0.0000$), and number of drug types ($P < 0.0000$), under treatment but still seizures ($P < 0.0000$) differed significantly. Partial seizure, symptomatic etiology, intractable seizures and polytherapy were more common in the ''continue drug/attack'' group.

Analysis of risk factors by logistic regression, shows drug withdrawal ($P < 0.001$), polytherapy ($P < 0.05$), presence of seizure before withdrawal ($P < 0.001$) and seizure etiology ($P < 0.0001$) were strongly associated with seizure recurrence after drug withdrawal.

Discussion

The SARS outbreak was a severe threat to the modern society. The uncertainty regarding how the disease spread, and the high mortality rate caused tremendous panic. The social and economic influence was more severe than that of natural disaster such as earthquake or hurricanes.

The sudden shutdown of the OPD was a great threat to the health care delivery system for many

patients. Although medical staff responded quickly by contacting scheduled patients by phone using the patient information lists and by mailing medication to the patients, many patients could not be contacted because of incomplete or incorrect contact information. Many patients in the ''lost contact'' group stopped taking drugs because of reluctance to contact the hospital, and interruptions in long-term treatment often result in seizures even status epilepticus.

Among the 290 cases included in this report, no sudden unexpected deaths were reported. In the excluded 44 cases, the seizures reoccurred in 3 of 10 self-report seizure free cases. They were excluded because of not keeping complete seizure record. Of the final 227 patients analyzed, 49 cases did not have medication. Twenty-eight of these cases suffered seizures during this period. Four cases were sent to ER because of frequent attacks and another two because of status epilepticus. Compared to the pre-SARS period, seizure frequency significantly increased during the SARS period. In these cases, the seizures were consistently controlled after antiepileptic drugs were re-instituted.

Previous reports have shown uncontrolled seizures and tonic–clonic seizures increased the rate of mortality[4] and sudden unexpected death.[9,10] Tonic–clonic seizures appeared to carry a greater risk of sudden unexpected death than partial seizures.[9,10] Fortunately, no fatalities were observed among our patients during this period. In the group of ''stop drug/attack'', more partial seizures were noted.

Drug withdrawal and compliance failure can cause seizures[6] or even status epilepticus.[7] We observed an increased frequency of seizures and status epilepticus in the group of ''stop drug/attack''. The odds ratio for risk of seizures in the drug withdrawal group is 3.14. Although 20 cases already had been seizure-free for at least 6 months, this group, compared to the ''stop drug/no attack'' group had more partial seizures, symptomatic etiologies, and multiple drug therapy. These findings were in accordance with the study of risk of recurrence after antiepileptic drug withdrawal: ''symptomatic etiology is a major risk for the recurrence of seizures''.[11]

Comparing the difference between the ''continue drug/no attack'' group and ''continue drug/attack'' group, the former group had more seizure-free patients in the pre-SARS period. This group also had more patients with idiopathic etiology and monotherapy. The former group's seizures were more easily controlled than the latter group. Although SARS caused great distress throughout society, these epilepsy patients suffered exceptional stress. Seizure frequency in these two groups did not increase during the SARS period. Previous report regarding the influence of a flooding natural disaster on epilepsy shows stress to be significant factor for provocation seizures.[12] In the present study, comparison of different time period showed no evidence that stress was an aggravating factor for their seizures in these patients.

The present study clear shows the SARS outbreak affected other medical diseases. The example of the drug withdrawal effects in epilepsy patients reflexes just one aspect of the overall impact of SARS outbreak. Other long-term diseases, such as renal failure or diabetes mellitus, might also have been seriously affected by SARS. We can conclude from present study that in the group of symptomatic etiologies, still had seizure during the treatment and polytherapy, the acute drug withdrawal will induce recurrence of seizures.

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