ARTICLE

Comorbidities associated with epilepsy and headaches

Comorbidades associadas às epilepsias e cefaleias

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ABSTRACT

Comorbidities are often associated with chronic neurological diseases, such as headache and epilepsy. **Objectives**: To identify comorbidities associated with epilepsy and headaches, and to determine possible drug interactions. **Methods**: A standardized questionnaire with information about type of epilepsy/headache, medical history, and medication was administered to 80 adult subjects (40 with epilepsy and 40 with chronic headache). **Results**: Patients with epilepsy had an average of two comorbidities and those with headache of three. For both groups, hypertension was the most prevalent. On average, patients with epilepsy were taking two antiepileptic medications and those with headache were taking only one prophylactic medication. Regarding concomitant medications, patients with epilepsy were in use, on average, of one drug and patients with headache of two. **Conclusions**: Patients with chronic neurological diseases, such as epilepsy and headaches, have a high number of comorbidities and they use many medications. This may contribute to poor adherence and interactions between different medications.

Key words: epilepsy, headache, drugs interaction.

RESUMO

As comorbidades geralmente estão associadas a doenças neurológicas crônicas, tais como cefaleia e epilepsia. **Objetivos**: Identificar comorbidades associadas à epilepsia e cefaleia e determinar as possíveis interações de drogas. **Métodos**: Questionário padronizado com informações sobre o tipo de epilepsia/cefaleia, os antecedentes médicos e as medicações foi aplicado a 80 indivíduos adultos (40 com epilepsia e 40 com cefaleia crônica). **Resultados**: Pacientes com epilepsia e cefaleia apresentaram uma média de duas e três comorbidades, respectivamente, sendo, para ambos, hipertensão arterial sistêmica a mais prevalente. Em média, os pacientes com epilepsia estavam em uso de duas medicações antiepilépticas; aqueles com cefaleia, uma medicação profilática. Em relação às medicações concomitantes, os pacientes com epilepsia estavam em uso, em média, de uma droga e os pacientes com cefaleia de duas. **Conclusões**: Pacientes com doenças neurológicas crônicas, como epilepsia e cefaleia, apresentam elevado número de comorbidades e utilizam grande número de medicações. Isso pode contribuir para diminuir a aderência ao tratamento e facilitar interações entre diversas medicações.

Palavras-Chave: epilepsia, cefaleia, interações medicamentosas.

Epilepsy and headache are the two most common neurologic disorders affecting individuals of all ages worldwide. They constitute an important health and socioeconomic problem[1,2]. Approximately 50 million people suffer from epilepsy[3], while in the adult population the prevalence of active headache is around 46%[2].

Drug treatment of epilepsy, with antiepileptic drugs, and headache, with prophylactic drugs, is prolonged in most cases (years to decades). Moreover, although for both pathologies it is recommended the use of a single antiepileptic or prophylactic drug, the use of polytherapy is very common[4-6]. Therefore, there is high risk of interactions between the drugs used for the primary neurologic disorder and other ones necessary throughout life for different acute or chronic conditions.

In the treatment of chronic diseases, such as epilepsy and migraines, it is important to know the side effects of the prescribed drugs, as well as their contraindications and interactions, since most patients will need at some point to use medications for other associated diseases[4-7].

Once they are diseases that affect individuals at any age, chronically, comorbidities are common in people with epilepsy and headache and they lead to the use of other medications, which are added to the primary neurological drugs. In subjects with migraine, the second most common type of chronic headache, a long list of comorbidities are reported,

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the most frequent are psychiatric, respiratory, and cardiovascular disorders[8]. Similarly, a recent study showed that up to 60% of patients with epilepsy take more than five different drugs, compared with 15% of the general population. This increases the likelihood of drug interactions, particularly when the antiepileptic medication induces hepatic metabolism, leading to a decreased level of other medications[4].

This study aimed at identifying comorbidities associated with epilepsy and chronic headaches and the frequency and type of medications used in order to determine possible drugs interactions.

METHODS

In this study, we interviewed 80 individuals followed at the Neurology Service of Campinas State University. The questionnaire consisted of information about the type of epilepsy or headache, drugs used to treat the neurological disease, current health and medical history, and other concomitant medications used. The interviews were conducted between August 2, 2010 and December 16, 2010.

Patients were divided into two groups. The first group (Group 1) comprised 40 people with epilepsy, who were submitted to the questionnaire. The second one (Group 2) consisted of 40 patients with chronic headache matched with respect to age and sex to the first group. This group was subjected to another questionnaire.

Patients included in this study were 18 years-old or more and with intact ability to answer the questionnaires. Patients with mental retardation, behavioral disorder or other evident abnormalities that could compromise the cooperation to respond the questionnaires were excluded. For Group 1, patients should have an established diagnosis of epilepsy for at least one year in the hospital. For Group 2, patients should have a diagnosis of headache for at least one year in the studied department and should not have epilepsy.

All patients included in this study signed the informed consent approved by the Ethics Committee of the Department of Neurology of Faculty of Medicine at Universidade Estadual de Campinas, Campinas SP, Brazil.

RESULTS

Demographic data

We interviewed 80 patients: 22 men and 58 women, with ages ranging from 21 to 86 years-old (medium of 48).

Group 1 was composed by 40 individuals with epilepsy (25 women), with ages raging from 21 to 79 years-old (medium of 46). Thirty-five patients were employed, two unemployed, and three retired.

Group 2 was composed by 40 individuals with chronic headache (33 women), with ages ranging from 26 to 86 years-old (medium of 49). Thirty-eight patients were employed, one retiree, and one unemployed.

In Group 1, 33 patients had the diagnosis of focal epilepsies (21 with temporal lobe epilepsy, eigth with extra-temporal epilepsy, and four with undetermined epilepsies) and six had the diagnosis of generalized epilepsy (four patients with juvenile myoclonic epilepsy and two with other types).

In Group 2, 19 patients had the diagnosis of migraine, two of tension-type headache, six of mixed headache (association of migraine and tension type headache), four of trigeminal neuralgia, and six patients had other types of headache (cervicogenic, post-traumatic and cluster headache).

Neurological disease and medication

Patients with epilepsy were using an average of two antiepileptic drugs (AEDs), ranging from zero to four drugs. The most used AED was carbamazepine (25 patients), followed by clobazam (13 patients).

Patients with chronic headache were using an average of one prophylactic drug, ranging from zero to three drugs. The most used prophylactic drugs were sertraline, fluoxetine, carbamazepine, and valproate (five patients with each of these drugs).

Comorbidities and medication

The health history questionnaire was divided into comorbidities and patients' complaints or symptoms. Nineteen patients with epilepsy reported other illnesses. The most common condition was hypertension. They informed an average of two comorbidities (ranging from zero to four) and another of two complaints or symptoms (ranging from zero to ten), as seen in Fig 1 and 2.

Twenty-two patients with chronic headache reported other illnesses. The most common condition was hypertension. They informed an average of three comorbidities (ranging from zero to seven) and another of two complaints or symptoms (ranging from zero to nine), as can also be seen in Fig 1 and 2.

Regarding the chronic use of medications related to the comorbidities, patients with epilepsy were using an average of one drug (ranging from zero to four). The most used was levothyroxine, followed by captopril. Considering the amount of drugs chronically used (drugs for epilepsy and comorbidities), 21 patients (52%) were taking two drugs, 16 (40%) were taking three or four drugs, and three (8%) were taking five or more drugs (Fig 3).

Patients with chronic headache were using an average of two drugs (ranging from zero to nine). The most commonly used drug was hydrochlorothiazide (six patients), followed by captopril (four patients). Considering the amount of drugs used chronically (drugs for headache and comorbidities), 24 patients (60%) were using medications, six (15%) were taking three or four drugs and ten (25%) were taking five or more (Fig 3).

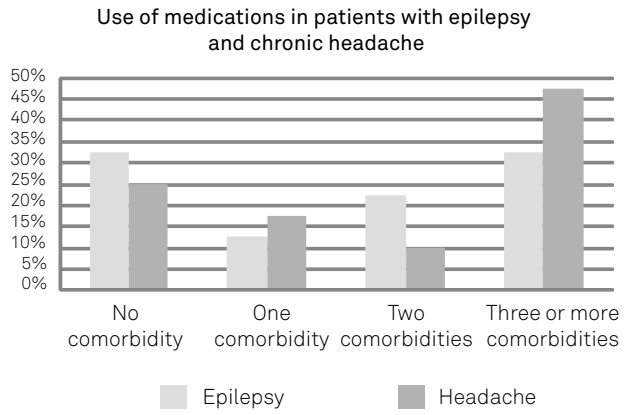

Fig 1. Percentage of patients with epilepsy and chronic headache, according to the number of comorbidities.

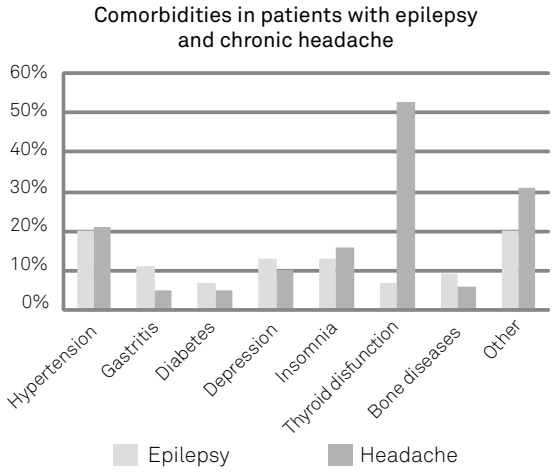

Fig 2. Frequency of different comorbidities in patients with epilepsy and chronic headache.

DISCUSSION

In this study, we verified that patients with epilepsy and chronic headache have a large number of other medical conditions and that the frequency of these comorbidities does not differ in both groups. We have also observed a large number of medications used by these patients for both the neurological disorder and the other diseases.

The importance of these facts lies in the high incidence of such diseases and in the fact that these neurological conditions require treatment for periods, ranging from years to decades and sometimes for the entire life. This leads to the possibility of poor adherence to the prescribed medication, drug interactions, and prejudice of the treatment.

Gidal et al., in a recent study, showed that up to 47% of men and 60% of women with epilepsy from 45 to 64 years-old take more than five drugs chronically, compared with 2% of men and 3% of women in the general population[4]. In this study, irrespective of age, 48% of patients with epilepsy and 40% of those with chronic headache were using three or more concomitant drugs.

Drug adherence is an important problem in chronically treated patients. The low adherence may have implications, such as inappropriate treatment, increasing of hospitalizations and even an increase of mortality in patients with epilepsy[9]. A survey showed that up to 70% of patients with epilepsy report missing doses[10]. The high number of drugs taken may significantly contribute to the decrease of adherence.

The other problem of concomitant use of many drugs in epilepsy patients is that the classical anti-epileptic drugs, such as carbamazepine, are known inducers of hepatic metabolism. Those drugs interfere with the effectiveness of drugs, such as steroids, warfarin, antibiotics, antipsychotics and antidepressants. For example, Oberndorfer et al. found a decreased efficacy of chemotherapy CCNU (lomustine) in patients receiving AED inducers of metabolism. In this study, patients with glioblastoma multiform that were using

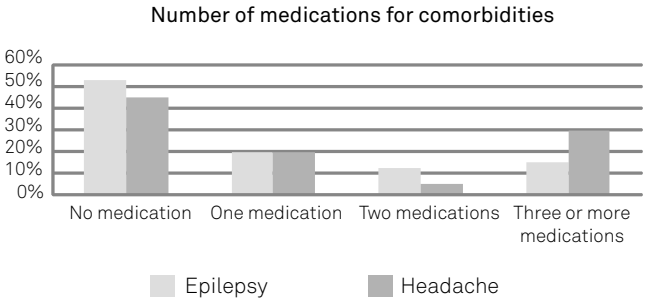

Fig 3. Percentage of patients with epilepsy and chronic headache, according to the number of medications used for comorbidities.

inducers AEDs had significant smaller survival rates than those in use of non-inducers AEDs[11].

The most used prophylatic medications for chronic headache in the studied patients were inhibitors of serotonin reuptake. These drugs are considered relatively safe and have low risk of interactions. However, some clinically relevant interactions may occur by inhibition of CYP isoenzymes, especially when in a regimen of multiple drugs, which is the case of our patients[12]. Serotonin reuptake inhibitors can also cause an increase in plasma levels of AEDs through inhibition of P450 2D6 isoenzyme[13]. As the concomitant administration of AEDs and serotonin reuptake inhibitors is common, therapeutic drug monitoring may be useful in designing correct and rational therapy, but further studies are necessary[13].

We can conclude by these data that patients with chronic neurological diseases, such as epilepsy and headaches, have a high number of comorbidities. These individuals are generally subject to the use of a large number of different medications, both for the neurological condition or comorbidities. This fact may contribute to poor adherence of these patients, besides being a risk for interactions between different medications.

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