

The epileptic multifactorial patient's burden. Review of the topic

José Pimentel

Epilepsy Unit, Department of Neurosciences,
Hospital de Santa Maria (CHLN), Faculty of Medicine,
Lisbon University

Received August 8, 2016
Accepted for publication on-line September 23, 2016
Published on-line September 30, 2016

Correspondence

José Pimentel, MD, PhD
Av. Prof. Egas Moniz
1649-035, Lisbon, Portugal
Phone: (351) 217 959 329
E-mail: josepimentel@fm.ul.pt

SUMMARY

Background. Approximately 26% of the burden of neurologic diseases is due to epilepsy. Its negative impact reflects mainly on people with epilepsy (PWE) themselves.

Aims. To highlight the negative impacts of epilepsy on the lives of PEW's so as to identify a realistic approach to their individual needs.

Methods. For recently published papers PubMed and MEDLINE databases were used. In addition relevant references mentioned in the searched articles were also considered.

Review and discussion. Generalized tonic-clonic seizures and refractory epilepsy are the most important factors burdening PWE's, resulting in increased injuries and mortality, including Sudden Unexpected Death in Epilepsy (SUDEP). The need of chronic intake of antiepileptic drugs (AEDs) and of epilepsy surgery are also important with regards to potential for side effects, drug interactions, and different surgery risks. PWE harbour more medical and psychiatric comorbidities than the general population and results in a decreased quality of life. Decreased self-esteem and major stigma are also frequent, linked to social, economic and personal negative consequences.

Age also plays a role, younger people being more stigmatized given the interdiction to drive or difficulty in getting a job. In the elderly, seizures may have an impact on mental status, mood and sleep. Gender may also contribute, particularly involving women in childbearing age, linked to the fear or depression due to the possibility of AED-induced fertility disturbances, foetal malformations, or breast feeding side-effects.

Conclusions. The burden that PWE face must be considered by all people involved in the management of their epilepsy. The causes may be multifactorial, all interconnected and each one influencing the others.

Key words: comorbidity • epilepsy • seizures • quality of life • social stigma

BACKGROUND

Epilepsy is one of the most frequent chronic neurological diseases. Its incidence is approximately 50 cases per 100 000 people per year, with a prevalence of 4 to 10 cases per 1000 habitants (Laxer et al., 2014). However, much higher numbers are reported for lower income countries. Indeed, incidences and prevalences up to 215 and 130, respectively, have been estimated for these countries (Newton and Garcia, 2012; Laxer et al.,

2014). Thus more (probably, much more) than 50 million people worldwide suffer from epilepsy (Laxer et al., 2014), and in Europe the number is approximately 6 millions (Villanueva et al., 2013).

Epilepsy was estimated to account for 0.5% of the global burden of disease, contributing to 7 307 975 disability-adjusted life-years, in 2005 (World Health Organization, 2006). The negative impact of epilepsy is

broad and extensive on its effects and to several levels, e.g., economic, relatives and or caregivers, and, mainly, the patient himself/herself. The physical risks of seizures are only one among the many burdens that may occur people with epilepsy (PWE). This fact must be taken into consideration when planning a therapeutic strategy which should not be guided only by the efficacy of antiepileptic drugs (AEDs), diet or surgery. Indeed, that many factors are interconnected with each being able to influence the others, may contribute to the patient's overall burden. Approximately 26% of the burden of neurologic diseases is due to epilepsy, calculated in disability-adjusted life-years (World Health Organization, 2014). The global burden of chronic epilepsy was considered greater than that of breast cancer for women and prostatic cancer for men in 2011 (World Health Organization, 2014).

This is a topic that concerns all ages of PWE, since childhood (Chong et al., 2016) to adulthood (Kerr, 2012), although with specific, age-related problems.

AIM

In this manuscript we want to present and comprehensively discuss the negative impacts of epilepsy in adult PEW's lives aiming to identify a full and realistic approach to their individual needs.

METHODS

A critical analysis of medical literature on the issue was conducted searching information from the PubMed and Medline databases. We also used articles in the Portuguese, English, French and Spanish language. The following words were searched: epilepsy comorbidities, epilepsy burden, epilepsy stigma, epilepsy mortality, and epileptic patient's burden.

REVIEW AND DISCUSSION

The impact of seizures per se and by their type and frequency

These are, for sure, the most important factors contributing to the burden that PWE's endure (Beghi et al., 2002). Seizures per se are a burden for PWE. However, it is reasonable to conclude that the occurrence of generalized tonic-clonic seizures (GTCS) and the lack of control of any type of seizures (refractory epilepsy) contribute to the highest burdens. Indeed, about 22.5% of PWE are drug-resistant, experiencing additional systemic and psychiatric comorbidities, stigma-

tization, reduced quality of life and increased mortality (Laxer et al., 2014).

Injuries

A European cohort study assessing the risk of epilepsy-related accidents showed that the cumulative probability of their occurrence at 12 months was 17% in PWE vs 12% in matched controls, whereas at 24 months percentages were 27% and 17%, respectively ($p < 0.0001$) (Beghi et al., 2002). A population-based study of hospital admissions following injuries reported that, among people receiving care within 48 h, those with epilepsy were three times more frequent than in the general population (24.2% vs 8.1%; relative risk 3.0; 95% confidence intervals 1.3, 4.7) (Télliez-Zenteno et al., 2008). It is also adequate to connect the injuries to the seizures type, GTCS deserving to be most of ten implicated.

Mortality

PWE harbours a mortality rate 2 to 3 times higher than general population and the cause appears to be related with the underlying aetiology (Kerr, 2012), like cerebrovascular diseases and cancer. Concerning the seizure type, GTCS, again, should also play an important role for this rate.

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death directly related to epilepsy. Its annual incidence is estimated to be 0.81 cases per 1 000 000 population, or 1.16 cases per 1000 PWE. It ranks second only to stroke comparing years of potential life lost from SUDEP with selected other neurologic diseases (Thurman et al., 2014). Among the several risk factors are GTCS, especially if intractable and occurring during the night (Tomson et al., 2005; Kerr, 2012).

Psychiatric and psychological health

A study aiming to investigate the relationship between psychological factors and epilepsy in a cohort of over 400 PWE found that, although stress, anxiety and depression were each significant predictors of change in seizure recency (i.e. time since last seizure; $p < 0.01$), depression mediated significantly the relationship of both anxiety and stress with change in seizures frequency ($p < 0.01$) and recency ($p < 0.01$) over time (Thapar et al., 2009). Hence, the influence of perceived stress and anxiety seems to be mediated by depression, although PWE considers stress as the most probably seizure trigger (Kerr, 2012).

Back to the importance of refractory seizures, mainly of the idiopathic generalized epilepsies (IGE), in the PWE's burden, a study comparing 19 PWE with this type of seizures with 23 with temporal lobe epilepsy (TLE) showed that attention/executive functioning (as measured by the Trail marking test) and intelligence (as measured by Wechsler Adult Intelligence Scale) were lower for the first group compared with the second (Sarkis et al., 2013). The conclusion was that people with IGE seems to have lower performance IQ, impaired performance on tests of executive functioning, and lower depression scores compared with people with TLE, suggesting different pathophysiological mechanisms.

The impact of treatment

Pharmacological

The need of taking AED for a long period of time may also contribute to the PWE's burden. Indeed, the potential for side effects, drug interactions and the stigma for having to receive them may all play a crucial role. Cross-sectional studies and randomized controlled studies showed that up to 90% of PWE experiences side effects which may account for up to 40% of treatment failures (Perucca et al., 2009; Kerr, 2012). AED interactions, either between them or with other drugs, may also potentiate this burden. In this respect, enzyme inducing AEDs, like some of the old generation (carbamazepine, phenobarbital and phenytoin) play an important role in this occurrence, whereas the great majority of those of the new generation are safer giving their better pharmacokinetic and pharmacodynamic profiles.

AED side effects, along with depression, were found to be by far the strongest negative predictors of health-related quality of live (QoL). An important conclusion of an extensive study with more than 900 PWE with refractory seizures was that, if seizures cannot be fully controlled, PWE are likely to benefit more from a therapeutic strategy aiming to avoid the burden of AED side effects rather than one aiming to fully control seizures or even to reduce them (Luoni et al., 2011).

Surgery

Although epilepsy surgery is associated with several and different risks according to the different modalities, e.g., resective or palliative, including neurostimulation, they are systematically very low (Laxer et al., 2014). Furthermore, when evaluating its risk-benefit not only the risks but also the patient realistic expectations (seizure freedom vs reduced seizures) must be considered.

Diet

When properly used, the various available diets are well tolerated with very low risks (Laxer et al., 2014). Moreover, it is a treatment still seldom used in adult PWE. However, the ketogenic diet may give rise to cumbersome culinary and social restrictions and potential side effects (Klein et al., 2014).

The impact on comorbidities

PWE are expected to harbour more AED-unrelated comorbidities, either medical or psychiatric, than the general population (Kerr, 2012). Often stroke, asthma, hearing and/or visual impairment, headache and digestive disturbances are the most frequently mentioned. The most frequent secondary complaints are depression, anxiety, panic and behaviour disorders (Gaitatzis et al., 2004; Villanueva et al., 2013).

The US National Comorbidity Survey Replication, including data from over 5500 individuals, reported that PWE are significantly expected to have at least one physical (93.6% vs 77.8%; $p < 0.001$; odds ratio 4.2) and mental (67.9% vs 47%; $p < 0.001$; odds ratio 2.1) comorbidity compared with people without epilepsy. Epilepsy strongly correlated with high (four or more) comorbid physical disorders (41.2%) compared with people without epilepsy (20.2%) (Kessler et al., 2012).

According to the fact that all PWE' burden causes are interconnected and able to influence each other, comorbidities have a strong impact on PWE overall health status and QoL with a significant association between the presence of comorbidities and a decreased QoL (Baumeister et al., 2005; Kerr, 2012).

The impact of stigmatization

Both suffering from epilepsy and the need to receive treatment contribute to decreased self-esteem and major stigma. This may be linked to social exclusion, school banishment, employment denial or even marrying impediment and high levels of divorce. Furthermore, they may pave the way to increased psychiatric comorbidities (Baker et al., 1997; Kerr, 2012).

The stigma experienced by PWE may be "felt", if it refers to the shame of having epilepsy and the fear of finding enacted stigma, or "enacted", if it means discrimination against PWE solely by the condition itself. (Fernandes et al., 2011; Kerr, 2012). "Felt" stigma is considered to be of more concern in developed countries, whereas "enacted" stigma will prevail in developing countries (Jacoby, 2008; Kerr et al., 2012).

The impact on quality of life

An observational, multicentre, retrospective study with patients with refractory seizures aiming to estimate the QoL and economic impact of this type of epilepsy (Villanueva et al., 2013) showed that PWE achieving seizure control (20.3%) presented better scores on used QoL questionnaires (QOLIE 31-P – 70.8 vs 56.4, $p < 0.0001$; EQ-5D-3L-75.6 vs 64.7, $p < 0.001$) and lower incidence of major depression (NDDIE scale – 23% vs 8.3%, $p < 0.05$)

Another retrospective study of 33 people with generalized epilepsy-juvenile myoclonic epilepsy-, followed-up for at least 20 years (Schneider-von Podewils et al., 2014) showed that early and long-term seizure control significantly improved both social adjustment ($p = 0.02$) and occupational integration ($p = 0.02$) and was associated with better QoL (odds ratio 2.25). In contrast, high seizure burden highly affected aspects of personal life-family and work-, and uncontrolled seizures significantly ($p = 0.02$) affected patient's employability.

Finally, another study, also with people with generalized epilepsies, was conducted in the United States, Europe and Brazil, aiming to understand their current burden on QoL. PWE were categorized into four categories according to seizure frequency, and QoL was measured using the SF-36v2 Mental (MCS) and Physical Component Summary (PCS) scores (Gupta et al., 2016). PWE within the two and three most frequent seizures categories reported worse MCS and PCS scores, worse healthy utility scores (e.g., visits to the general practitioner/emergency room) and greater "presenteeism" (attending work while mentally or physically inability to work)

Impact of age

Age groups may contribute with different weight for the PWE's burden. Younger people may be more stigmatized and harbour more psychiatric comorbidities given the interdiction to drive, school banishment or difficulty in getting a job. In opposition, physical comorbidities may be less relevant given the usual general robust health of this particular age group.

In the elderly, in general with one or more systemic diseases and under several drugs, higher AEDs side-effects and drug interactions should be expected. However, seizures themselves may have impact on mental status, mood and sleep in this age group. A study explored these three topics in elderly patients compared to age and gender matched community controls with-

out epilepsy (Hant et al., 2009). Tests included a mental status test, the Blessed Information Memory and Concentration (BIMC) test, Prime-MD Patient Health Questionnaire (PHQ) Depression and Anxiety Modules, and Outcomes Study Sleep Scale. Mean PHQ Depression scores were higher for cases than controls (4.2 vs 0.8; $p = 0.006$) and 18% of the cases vs none in controls met screening criteria for depression. Mean PHQ Anxiety scores were also higher for cases than controls (3.7 vs 0.0; $p = 0.001$). Finally, cases showed poorer sleep scores in the categories of somnolence ($p = 0.009$), and shortness of breath/headache ($p = 0.021$). Hence, decreased mental status, higher prevalence of depression and poorer sleep health may be found in this particular age and is unrelated to epilepsy medication or mood disturbances.

Impact of gender

The best example is that of women in childbearing age. Indeed, the possibility of foetal malformations may give rise to a strong feeling of fear in becoming pregnant or even to decide to prevent pregnancy from occurring. The same feeling may occur during pregnancy, delivery and breast feeding given the possible occurrence of disturbances in women taking AEDs. AEDs may also result in fertility disturbances. All these negative factors may stigmatize these women, give rise to serious comorbidities, like depression, and bring marriage conflicts and decrease QoL.

An interesting study carried out in Zambia (Elafros et al., 2013) which included 100 mothers with epileptic children showed that 20% of them felt stigmatized because of their child's epilepsy, and that higher maternal stigma was associated with lower familial and community support (ORS: 65.2 and 34.7, respectively; both $p = 0.002$) as well as an increased in psychiatric morbidity. However, increased education and epilepsy knowledge was found to decrease mother stigmas (ORS: 0.8 and 0.7, respectively; both $p < 0.001$).

CONCLUSIONS

PWE's burden is a reality that must be faced by all people involved in the management of epilepsy, included PWE themselves and their caregivers. Several causes may contribute to this burden, all of them interconnected and each one able to influence the others.

Not surprisingly, uncontrolled epilepsy, accounting for nearly one third of PWE, is the most important contributing factor, mainly if GTCS. Indeed, the risk of

hospitalizations due to injuries, of mortality (including SUDEP) and the impact on mental health is much higher for generalized convulsive refractory seizures.

The burden in lower-income countries is more than twice that found in higher-income countries, given the fact of the risk factors being also higher. Also, the treatment gap for epilepsy is high in poorer areas (Newton and Garcia, 2012).

Effective management of epilepsy should be based on the individual needs and expectations of each PWE and their caregivers, ensuring that they receive the appropriate care and the right information and support in order to achieve the best daily life as possible

As general practitioners (GP) are on the "frontline" of the PWE care, they should be involved in the management of this problem, giving them the right information to be alert for, and to cope with it. All clinicians, either GPs or neurologists/epileptologists should include assessments of epilepsy comorbidities, stigmatization and quality of life as complement of the treatment strategies of PWE.

CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interest to declare.

REFERENCES

- Baker G.A., Jacoby A., Buck D., Stalgis C., Monnet D.: Quality of life of people with epilepsy: a European study. *Epilepsia*, 1997, 38: 353–362.
- Klein P., Tyrlikova I., Mathews G.C.: Dietary treatment in adults with refractory epilepsy: a review. *Neurology*, 2014, 83: 1978–1985.
- Gaitatzis A., Carroll K., Majeed A., Sander J.W.: *The epidemiology of the comorbidity of epilepsy in the general population*. *Epilepsia*, 2004, 45: 1613–1622.
- World Health Organization (WHO): *Disease Burden: Regional Estimates for 2011*. Available at www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index1.html, Accessed Jan.7, 2014.
- Baumeister H., Balke K., Harter M.: Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. *J. Clin. Epidemiol.*, 2005, 58: 1090–1100.
- Beghi E., Cornaggia C., REST-1 Group.: *Morbidity and accidents in patients with epilepsy: results of a European cohort study*. *Epilepsia*, 2002, 43: 1076–1083.
- Chong L., Jamieson J.J., Gill D., Singh-Grewal D., Craig C., Angela J.U.: *Children's experience of epilepsy: A systematic review*. *Pediatrics*, 2016, 138 e20160658; DOI-10.1542/peds.2016–0618.
- Elafros M.A., Sakubita-Simasihu C., Atadzhanov M., Haworth A., Chomba E., Birbeck G.L.: Stigma and psychiatric morbidity among mothers of children with epilepsy on Zambia. *Int. Health*, 2013, 5: 288–294.
- Fernandes C.T., Snape D.A., Beran R.G., Jacoby A.: *Epilepsy stigma: what do we know and where next?* *Epilepsy Behav.*, 2011, 22: 55–62.
- Gupta S., Kwan P., Faught E., Tsong W., Forsythe A., Ryvlin P.: *Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: An analysis from the National Health and Wellness Survey*. *Epilepsy Behav.*, 2016, 55: 146–156.
- Hant S.R., Katz M., Masur J., Lipton R.B.: *Seizures in the elderly: impact on mental status, mood and sleep*. *Epilepsy Behav.*, 2009, 14: 540–544.
- Jacoby A.: *Epilepsy and stigma: an update and critical review*. *Curr. Neurol. Neurosc. Rep.*, 2008, 8: 339–344.
- Kerr M.P.: *The impact of epilepsy on patients' lives*. *Acta. Neurol. Scand.*, 2012, 126 (Suppl. 194): 1–9.
- Kessler R.C., Lane M.C., Shahly V., Stang P.E.: Accounting for comorbidity in assessing the burden of epilepsy among US adults: results from the National Comorbidity Survey Replication (NCS-R). *Mol. Psychiatry*, 2012, 17: 748–758.
- Laxer K.D., Trinkka E., Hirsch L.J., Cendes F., Langfitt J., Delanty N. et al.: The consequences of refractory epilepsy and its treatment. *Epilepsy Behav.*, 2014, 37: 59–70.
- Luoni C., Bisulli F., Canevini M.P., SOPHIE Study Group et al.: *Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments*. *Epilepsia*, 2011, 52: 2181–2191.
- Newton C.R., Garcia H.H.: *Epilepsy in poor regions of the world*. *Lancet*, 2012, 380: 1193–1201.
- Perucca E., Gilliam F.G., Schmitz B.: *Epilepsy treatment as a predeterminant of psychological ill health*. *Epilepsia Behav.*, 2009, 15 (Suppl. 1): S46–S50.
- Sarkis R.A., Pietras A.C., Cheung A., Baslet G., Dworetzky B.: *Neuropsychological and psychiatric outcomes in poorly controlled idiopathic generalized epilepsy*. *Epilepsy Behav.*, 2013, 28: 370–373.
- Schneider-von Podewils F., Gasse C., Geithner J., Wang Z.I., Bombach P., Berneiser J. et al.: *Clinical predictors of long-term social outcome and quality of life in juvenile myoclonic epilepsy: 20–65 years of follow-up*. *Epilepsia*, 2014, 55: 322–330.
- Téllez-Zenteno J.F., Hunter G., Wiebe S.: *Injuries in people with self-reported epilepsy: a population-based study*. *Epilepsia*, 2008, 49: 954–961.
- Thapar A., Kerr M., Harold G.: *Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures*. *Epilepsia*, 2009, 14: 134–140.

Thurman D.J., Hesdorffer D.C., French J.A.: *Sudden unexpected death in epilepsy: Assembling the public health burden*. *Epilepsia*, 2014, 55: 1479–1485.

Tomson T., Walczac T., Sillanpaa M., Sander J.W.: *Sudden unexpected death in epilepsy: a review of incidence and risk factors*. *Epilepsia*, 2005, 46 (Suppl. 11): 54–61.

Villanueva V., Girón J.M., Martín J., Hernández-Pastor L.J.,

Lahuerta J., Doz M. et al.: *Quality of life and economic impact of refractory epilepsy in Spain: The ESPERA Study*. *Neurologia*, 2013, 28: 195–204.

World Health Organization (WHO): *Neurological Disorders: Public Health Challenges*. World Health Organization, Geneva 2006.

