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Review

The consequences of refractory epilepsy and its treatment

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ABSTRACT

Seizures in some 30% to 40% of patients with epilepsy fail to respond to antiepileptic drugs or other treatments. While much has been made of the risks of new drug therapies, not enough attention has been given to the risks of uncontrolled and progressive epilepsy. This critical review summarizes known risks associated with refractory epilepsy, provides practical clinical recommendations, and indicates areas for future research. Eight international epilepsy experts from Europe, the United States, and South America met on May 4, 2013, to present, review, and discuss relevant concepts, data, and literature on the consequences of refractory epilepsy. While patients with refractory epilepsy represent the minority of the population with epilepsy, they require the overwhelming majority of time, effort, and focus from treating physicians. They also represent the greatest economic and psychosocial burdens. Diagnostic procedures and medical/surgical treatments are not without risks. Overlooked, however, is that these risks are usually smaller than the risks of long-term, uncontrolled seizures. Refractory epilepsy may be progressive, carrying risks of structural damage to the brain and nervous system, comorbidities (osteoporosis, fractures), and increased mortality (from suicide, accidents, sudden unexpected death in epilepsy, pneumonia, vascular disease), as well as psychological (depression, anxiety), educational, social (stigma, driving), and vocational consequences. Adding to this burden is neuropsychiatric impairment caused by underlying epileptogenic processes ("essential comorbidities"), which appears to be independent of the effects of ongoing seizures themselves. Tolerating persistent seizures or chronic medicinal adverse effects has risks and consequences that often outweigh risks of seemingly "more aggressive" treatments. Future research should focus not only on controlling seizures but also on preventing these consequences.

1. Risks of refractory or uncontrolled epilepsy

More than 50 million people worldwide suffer from epilepsy [1]. Each year, 16 to 134 new-onset epilepsy cases per 100,000 people add to the global burden of epilepsy [2,3]. In a population-based study conducted in Western Europe, the epilepsy in 22.5% of all patients was found to be drug-resistant [4]. Patients with drug-resistant epilepsy account for most of the burden of epilepsy in the population [5] because of the substantial frequencies at which they experience comorbid illnesses [6,7], psychological dysfunction [8], social stigmatization [9], reduced quality of life and increased risk of mortality [10–12], and, ultimately, a decreased life expectancy [6,13]. Therefore, treatment efforts must aim for full seizure control, especially for generalized tonic–clonic seizures. Diagnostic procedures and medical and surgical treatments are not without their own risks [14–19]. However, these risks are usually smaller than the risks of uncontrolled, progressive, or drug-resistant epilepsy. Moreover, these risks must be explained to patients carefully, such that informed treatment decisions can be made.

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1.1. Epidemiology

The incidence of epilepsy in developed countries is approximately 50 per 100,000 individuals per year, with the greatest rates for infants and the elderly [2,20]. In developing and resource-poor countries, where most people do not receive adequate treatment, the incidence is usually greater than 100 per 100,000 individuals per year [2,21]. A decline in the incidence of childhood epilepsy has been observed during the past 30 years in developed countries, but this has been paralleled by an increase in the incidence of epilepsy in the elderly [22,23]. The prevalence of epilepsy in developed countries ranges between 4 and 10 per 1,000 individuals per year [2,20,21], with much greater prevalence rates in developing and resource-poor countries [2], and some estimates at greater than 130 per 1000 individuals per year [3,24].

The seizures in approximately two-thirds of people with epilepsy can be successfully controlled with currently available antiepileptic drugs (AEDs), leaving one-third with uncontrolled epilepsy [25]. The temporal patterns of epilepsy, with a substantial number of patients following a relapsing–remitting course [26,27], can render early identification of patients with drug-resistant epilepsy a difficult task and may explain delays in referrals to epilepsy surgery centers [28,29]. Although up to 24% of patients with drug-resistant epilepsy can achieve remissions for more than 1 year [30–33], physicians should not withhold referral for presurgical evaluation, since two randomized controlled studies have clearly shown superiority of surgical treatment versus continuous medical treatment [34,35]. Based on these studies, the number of patients with temporal lobectomy needed to treat to render one patient completely seizure-free after years of chronic disabling seizures is <2 [34,35]. A delay in referral increases the burden of epilepsy for the overall population, and reduces life spans and quality of life for individual patients.

1.2. Drug resistance and its clinical predictors

In 2010, the International League Against Epilepsy published a consensus definition of drug-resistant epilepsy that aimed to improve patient care and facilitate research, and which should ultimately lead to earlier identification of and better delineation of the syndromes associated with drug resistance [36]. The definition of drug resistance encompasses two hierarchical levels. Level 1 provides a general scheme to categorize response to interventions as seizure freedom, treatment failure, or undetermined, on the basis of standard criteria. Level 1 provides the basis for Level 2 determinations, which form the core definition of drug-resistant epilepsy "as a failure of at least two tolerated, appropriately chosen and used" AED regimens "to achieve sustained freedom of seizures [36]." According to the "rule of three" for calculating confidence intervals for zero events [37], "sustained seizure freedom" requires that the patient be seizure-free for at least three-times the longest interseizure interval before the intervention, or at least 12 months, whichever is greater [36]. This definition conceptualizes drug resistance as a dynamic phenomenon, also allowing for remission over time [26], which can be observed at an annual rate of 4% for adults in prospective series and at even greater rates for children [38–40].

Besides the number of failed AEDs (which is used as a definition criterion), the most consistent predictors of refractory epilepsy are a high frequency of seizures in the early phase of the disease, a neurologic deficit at disease onset, and a structural cause of the epilepsy, as evidenced by MRI [39,41–43]. However, uncontrolled epilepsy is not always drug-resistant [44], and pseudoresistance due to incorrect diagnosis, inappropriate AED, or inappropriate dosage must be ruled out before a patient's seizures can be considered drug-resistant [45–50].

1.3. Burden of refractory epilepsy

The impact of epilepsy on an individual's life is a combination of physical consequences of seizures, effects on social position, and psychological outcomes of both. An estimated 26% of the burden of neurologic disorders is caused by epilepsy, calculated in disability-adjusted life-years (DALYs) [51]. In 2011, the global burden of chronic epilepsy for women was greater than that of breast cancer, and was nearly four-times greater than the burden of prostate cancer for men [51]. This calculation includes premature deaths and the loss of healthy life because of disability. However, it does not factor the effects of stigma and social exclusion or their repercussions on families [9,52].

2. Epilepsy and mortality

Mortality is greater for those with epilepsy than for those without for many reasons, including sudden unexpected death in epilepsy (SUDEP), accidents, suicide, vascular disease, pneumonia, and factors directly related to the underlying causes (e.g., brain tumors, neurodegenerative disease). Within epilepsy, mortality is greatest for those with *refractory* disease. Although this excess mortality has been long-recognized, many large, high-quality studies (all published in 2013) have provided important details about the magnitude of the problem, consistent findings between countries, and specific causes [12,53–61]. Overall, people with epilepsy have a 1.6- to 11.4-times greater mortality rate than expected [55,56,62]. In childhood-onset epilepsy, the standardized mortality ratio (SMR) is 5.3–9.0 [59,63,64]. In a study of 245 children with epilepsy in Finland followed for 40 years, 24% had died (3 times the expected rate) [64]. Cumulative mortality was 37% for those with symptomatic epilepsy and 12% for those with idiopathic/cryptogenic epilepsy (Fig. 1) [64]. Of the 107 patients not in terminal remission (i.e., not seizure-free for the last 5 years), 48% had died. The only multivariate predictor of survival was 5-year terminal remission of seizures [64].

In an older study of 564 newly diagnosed patients from the United Kingdom, those with symptomatic epilepsy had up to a 10-year shorter life expectancy than those without epilepsy [6]. Further, those with epilepsy of unknown cause had up to a 2-year shorter life expectancy [6]. A later follow up of the same cohort for 20 to 25 years found a SMR of 2.55 overall, with a 3.68 SMR (3.05–4.42) for those with symptomatic epilepsy, and a 1.66 SMR (1.33–2.06) for those with idiopathic/cryptogenic epilepsy [65]. These SMRs remained significantly increased 20 to 25 years after diagnosis, despite greater than 70% of patients being in remission. In a very large study of 69,995 people with epilepsy in Sweden followed for an average of 9 years, 8.8% had died, with a median age of 34.5 years at time of death. The adjusted odds ratio for mortality was 11.1 versus the general population and 11.4 compared with unaffected siblings (Table 1) [55].

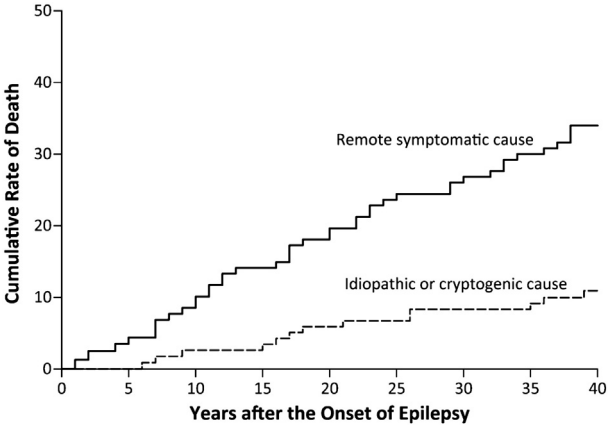

Fig. 1. Cumulative rate of death according to cause of epilepsy. Copyright © 2010 N Engl J Med. Reproduced with permission from Massachusetts Medical Society.