Drug Resistance in Late-onset Epilepsy

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ABSTRACT **Background:** The annual incidence of epilepsy increases with age, from nearly 28 per 100,000 by the age of 50 years to 139 per 100,000 by the age of 75 years. Late-onset epilepsy differs from epilepsy at a young age in the prevalence of structural-related epilepsy, types of seizures, duration of seizures, and presentation with status epilepticus.

Objectives: To check the response to treatment in patients with epilepsy with age of onset of 50 years and older.

Methods: We conducted a retrospective study. The cohort included all patients referred to the Rambam epilepsy clinic between 1 November 2016 and 31 January 2018 with epilepsy onset at age 50 years or older and at least one year of follow-up at the recruitment time point and epilepsy not caused by a rapidly progressive disease.

Results: At recruitment, most patients were being treated with a single antiseizure medication (ASM); 9 of 57 patients (15.7%) met the criteria for drug-resistant epilepsy (DRE). The mean duration of follow-up was 2.8 ± 1.3 years. In an intention-to-treat analysis, 7 of 57 patients (12.2%) had DRE at the last follow-up.

Conclusions: Late-onset epilepsy, which is defined as a first diagnosis in patients older than 50 years of age, is easy to control with monotherapy. The percentage of DRE in this group of patients is relatively low and stable over time.

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KEY WORDS: drug-resistant epilepsy, epilepsy in the elderly, epilepsy prognosis in older adults, late-onset epilepsy

Epilepsy is one of the most common neurological disorders. The annual incidence of epilepsy increases with age from nearly 28 per 100,000 by the age of 50 years to 40 per 100,000 by the age of 60 years and to 139 per 100,000 by the age of 75 years [1].

Late-onset epilepsy differs from epilepsy at a young age in the prevalence of structural-related epilepsy, types of seizures, duration of seizures, and presentation with status epilepticus. There are a few randomized controlled studies on the appropriate treatment for this group of patients, with results supporting a good response to antiseizure medications (ASM), but still prospective randomized controlled trials with large samples are lacking [2]. Over the last several years, many reviews have dealt with ASM treatment in elderly patients, but most did not focus on late-onset epilepsy [1].

In this study, we evaluated epilepsy patients with age of onset of 50 years or older, and characterized their disease regarding etiology, duration, and response to treatment.

PATIENTS AND METHODS

Our study is a historical cohort design. Inclusion criteria included age over 50 years, onset of epilepsy after 50 years of age, at least one year of follow-up after recruitment, and epilepsy not caused by a rapidly progressive disease such as a high-grade glioma tumor. The cohort included all patients referred to the Rambam epilepsy clinic between 01 November 2016 and 31 January 2018 and who fulfilled the inclusion criteria.

The diagnosis of epilepsy was in accordance with the International League Against Epilepsy (ILAE) consensus [3]. Epilepsy etiologies were classified according to the ILAE update as structural, metabolic, genetic, infectious, immune, and unknown [4]. Due to the growing importance of neurodegenerative diseases, we added a neurodegenerative category [5]. Seizure types were classified according to the ILAE update [4].

Imaging results were classified as benign space occupying lesion, post-meningioma excision encephalomalacia, post-traumatic encephalomalacia, post-encephalitis encephalomalacia, post-stroke lesions, foreign body, T2 limbic high intensity, cavernoma, microangiopathic changes, atrophy, and normal.

Interictal electroencephalogram results were classified as left temporal epileptiform discharges, right temporal epileptiform discharges, right frontal epilpetiform discharges, bifrontal epileptiform discharges, generalized epileptiform discharges, focal background slowing, general background slowing, normal, and not conducted.

Demographic and clinical data were extracted from patient files. The frequency of seizures over the past year was examined at the recruitment visit and the last follow-up. Each patient was instructed to document the dates of seizures (by diary, list, or cell phone) and to report them at a follow-up visit.

Patient treatment responses were classified as respond-

ers, which was defined as no seizures in the last year either on monotherapy or polytherapy, or as drug-resistant epilepsy (DRE). DRE was defined as the failure of adequate trials of two ASMs tolerated and appropriately chosen and used (whether monotherapies or in combination) to achieve sustained seizure freedom for at least one year was also included [6].

We conducted the first analysis of ASM responsiveness at recruitment. The recruitment visit was defined as the first visit between 01 November 2016 and 31 January 2018, with a follow-up of at least one year before.

In May 2021, we conducted a second ASM responsiveness analysis. The outcome was measured as a treatment analysis of the patient's last follow-up. Descriptive statistics were performed using Microsoft Excel™ 2016 for Windows (Microsoft® Corporation, Redmond, WA, USA). The institutional review board of Rambam Health Care Campus approved all data collection and study procedures.

RESULTS

Of the 1080 patients followed during the study period, 159 were older than 50 years. In 63 patients, the age of onset was above 50 years. Two patients had rapidly progressive neurological disease, two had less than 1 year of follow-up, and two had less than 1 year of epilepsy diagnosis during the recruitment period. In total, 57 patients met the inclusion criteria and were included in the final analysis.

The mean age of the patients at the time of recruitment was 69.12 ± 6.89 (range 54–85) years, and the mean duration of epilepsy at the time of recruitment was 6.48 ± 5.3 (range 1–18) years.

Fifty-five patients had focal epilepsy and one patient had generalized epilepsy. In one patient, epilepsy could not be classified. Most of the patients had focal seizures with impaired awareness and focal seizures that evolved to bilateral convulsive seizures. Table 1 shows the demographic data of the patients and the data of epilepsy.

All patients underwent a brain magnetic resonance imaging scan, except for two who had heart pacemakers, as well as a computed tomography scan. Table 2 summarizes the imaging results of the patients. All patients underwent an interictal electroencephalogram test, except for 11 who had clear semiology in correlation with a clear lesion on imaging [Table 3]. The most common etiology of epilepsy was structural, followed by unknown. Figure 1 summarizes the different etiologies of epilepsies.

At recruitment, 40 patients were treated with a single ASM. The most common drug taken was lamotrigine, followed by levetiracetam and carbamazepine. Nine of 57 patients (15.7%) met the criteria for DRE. All patients had at least one follow-up after recruitment. The mean duration of recruitment follow-up was 2.8 ± 1.3 (range 1–4) years.

In an intention-to-treat analysis, 39 patients were treated with a single ASM at the last follow-up. The most common drug used was lamotrigine, followed by levetiracetam and carbamazepine. Seven of 57 patients (12.2%) met the DRE criteria. Figure 1 shows the patient outcomes at recruitment and at the last follow-up.

Table 1. Patient demographic and clinical data

Characteristic	Value
Mean age	69.12 ± 6.89 years
Female:Male	29:28
Mean epilepsy duration on recruitment	5.5 ± 4.5 years
Mean follow-up on recruitment	6.48 ± 5.3 years
Mean follow-up from recruitment to last follow-up	2.8 ± 1.3 years
Type of epilepsy	55 Focal 1 Generalized 1 Unclassified

Table 2. Imaging results

Imaging results	Number of patients
Benign space occupying lesion	3% (2 patients)
Post-meningioma excision encephalomalacia	19% (11 patients)
Post-traumatic encephalomalacia	9% (5 patients)
Post-encephalitis encephalomalacia	3% (2 patients)
Post-stroke lesions	12% (7 patients)
Foreign body	2% (1 patient)
T2 limbic high intensity	2% (1 patient)
Cavernoma	4% (2 patients)
Microangiopathic changes	7% (4 patients)
Atrophy	2% (1 patient)
Normal	37% (21 patient)

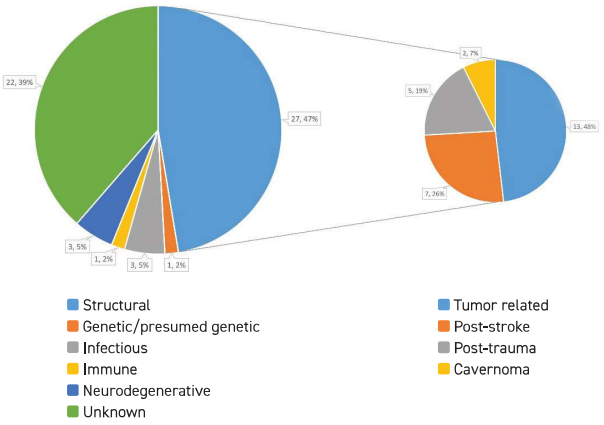
Table 3. Interictal electroencephalogram results

Interictal electroencephalogram results	Number of patients
Left temporal epilpetiform discharges	20% (11 patients)
Right temporal epilpetiform discharges	12% (7 patients)
Right frontal epilpetiform discharges	5% (3 patients)
Bifrontal epilpetiform discharges	5% (3 patients)
Generalized epilpetiform discharges	2% (1 patient)
Focal background slowing	12% (7 patients)
General background slowing	2% (1 patient)
Normal	23% (13 patients)
Not conducted	20% (11 patients)

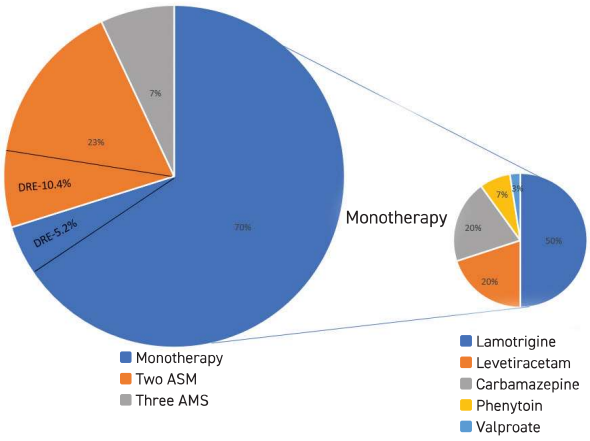
Figure 1. Etiologies of epilepsies and patient outcomes

ASM = antiseizure medication, DRE = drug-resistant epilepsy

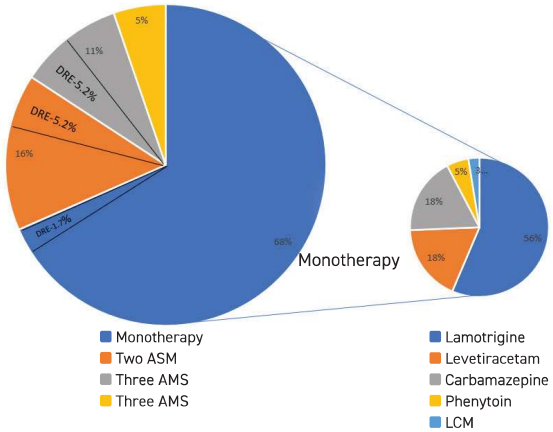
[A] All etiologies



[B] Patient outcome at recruitment



[C] Patient outcomes at last follow-up



DISCUSSION

Most of the patients in our cohort were ASM responders; only 12–15% of the patients had DRE. Furthermore, responses of most responders were easily controlled with a single ASM.

The percentage of DRE in our cohort is much lower than that reported in previous studies (20–40%) [6].

At the clinical level, four different forms of DRE were described:

DRE de novo:

- Epilepsy from its onset and throughout its course does not respond to ASM
- Delayed DRE: Epilepsy responds to ASM at its initial stage, with DRE development during later stages and a possible latency period of several years
- Fluctuating DRE: with periods of good responsiveness to ASM and lack of responsiveness
- Initial DRE with subsequent response to ASM [7]

Berg and colleagues [8] showed that there could be an early stage of childhood with good ASM responsiveness in patients with DRE of the temporal lobe. Children can even be weaned from ASM without exacerbation of seizures and only years later, sometimes even 20 years later, develop DRE.

The mean duration of epilepsy in our cohort at recruitment was 6.48 ± 5.3 (1–18) years. Only four patients had epilepsy diagnosed in the last year. However, only a small percentage of our patients had epilepsy for more than 15 years, so the small percentage of DRE patients may be related to the latency phenomena in the development of DRE. However, according to Brodie et al. [9], 24.7% of patients with new-onset epilepsy never entered seizure remission from the start; therefore, the number of DRE in our study is still low compared to the epileptic population in general.

Studies examining the causes of DRE showed that young age of onset, structural-metabolic related epilepsy, developmental disorder, neuropsychiatric disorders, prolonged febrile seizures, and epileptic status were associated with an increased risk of developing DRE [10]. Most of the patients in our cohort presented with structural-related epilepsy but had fewer other risk factors for the development of DRE.

Several studies have shown that high seizure frequency before ASM administration is an essential factor in DRE development [11]. It should be noted that several patients in our cohort who had daily seizures before starting ASM went into complete remission under monotherapy.

No hypothesis adequately explains DRE, which is probably related to the interaction between pharmacological mechanisms, disease mechanisms, and genetic predisposition [12,13].

Suggested pharmacological mechanisms include the target hypothesis, according to which DRE results from alternations that occur over time in the specific target of the drug, which makes the drug site of action not responsive to the drug [14]. An alternative

explanation is the transporter hypothesis, in which DRE is related to the expression of BBB efflux transports that prevent the appropriate ASM accumulation in the brain [13]. Disease-suggested mechanisms, such as the neural network hypothesis suggest that epilepsy causes structural alterations over time, making the regular network more susceptible to seizures [15].

Another disease-related explanation is the intrinsic severity hypothesis, which postulates that DRE is related to intrinsic factors within the cause of epilepsy. This theory suggests that the frequency of seizures before the onset of treatment is the best marker for DRE development [16].

Some researchers have suggested that modulation of ASM targets by genetic and epigenetic mechanisms may cause ASM ineffectiveness. A good example would be Dravet syndrome, in which the change in SCN1A is, on the one hand, the cause of epilepsy and, on the other hand, the cause of resistance to serval ASM dependent on the type of mutation [17]. In our opinion, DRE results from possible interactions between all of these factors.

The percentage of DRE in our cohort was small, probably due to several factors. Most of the patients had a localized lesion; therefore, the intrinsic severity of epilepsy was probably low. Most of the patients did not have long-lasting epilepsy; therefore, mechanisms that evolve over time, such as the target or transport hypothesis, are less likely. Most of the patients had acquired structural-related epilepsy; therefore, the hypothesis of a gene variant is less likely. The age of onset is an essential factor in the development of DRE and dependent on the intrinsic severity of epilepsy and the plasticity of the brain exposed to epilepsy. Since we expect to see more localized epilepsy and less plasticity in our group of patients, our patients reacted better to ASM with a lower percentage of DRE.

Our study had several limitations. First, it was a retrospective study. Second, the sample size was small, and last, there was no control group.

Most of the patients with epilepsy in our region are treated by neurologists in community clinics. Our epilepsy clinic is in an ambulatory tertiary hospital service, which sees patients who are more difficult to manage compared to a community clinic; therefore, we assume that the percentage of DRE patients in our group is even higher than the percentage of DRE in the general group of patients with epilepsy onset above 50 years.

CONCLUSIONS

Late-onset epilepsy, which is defined as a first diagnosis in patients older than 50 years of age, is easy to control with monotherapy. The percentage of DRE in this group of patients is relatively low and stable over time.

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We are so vain that we even care for the opinion of those we don't care for.
Marie von Ebner-Eschenbach (1830–1916), writer