Epilepsy & Behavior Reports 24 (2023) 100628

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

# Characteristics of an advanced epilepsy treatment gap in a region in Japan

Tetsuhiro Fukuyama [a,b,*], Manami Yabe [a], Makoto Nishioka [a], Takenori Natsume [a], Yuumi Hoshino [b,c], Kohei Kanaya [b,d], Kyoko Takano [e], Norimoto Kobayashi [f], Yushi Inoue [g]

[a] Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan
[b] Division of Epilepsy, Shinshu University Hospital, Matsumoto, Japan
[c] Department of Neurology, Shinshu University School of Medicine, Matsumoto, Japan
[d] Department of Neurosurgery, Shinshu University School of Medicine, Matsumoto, Japan
[e] Center of Medical Genetics, Shinshu University Hospital, Matsumoto, Japan
[f] Department of Pediatrics, Nagano Red Cross Hospital, Nagano, Japan
[g] National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Japan

ARTICLE INFO

*Keywords:*
Advanced epilepsy treatment gap
Epilepsy care system
Pseudo-drug-resistant epilepsy
Specialised epilepsy care

ABSTRACT

To investigate the quality of epilepsy care in a region in Japan that lacked specialised care, we retrospectively evaluated patients who visited our newly established epilepsy division between April 2018 and March 2021, and had been treated with anti-seizure medications (ASMs) for at least 1 year prior.

Of the 231 patients included, 169 had ongoing seizure episodes at first visit (seizure-persist group) and 62 had no seizure episodes for more than a year (seizure-free group). Eighty-three patients in the seizure-persist group had not received specialised epilepsy care, 15 had been treated with unnecessary medications, and seven had experienced side effects from ASMs. Twelve patients in the seizure-free group had been treated with unnecessary ASMs, 10 had been treated with ASMs with teratogenic potential and four had experienced ASM side effects. These patients could be classified as having an advanced epilepsy treatment gap (ETG) because they had not previously received necessary specialised care. The progressive decline in the number of patients with advanced ETG suggests that our new epilepsy division has addressed this issue.

This study highlights that a significant number of patients with advanced ETGs exist in Japan and that proper countermeasures are required to address this gap.

## Introduction

An epilepsy treatment gap (ETG) remains a major problem worldwide as its causes are heterogeneous across different regions and countries [1]. The conceptual definition of an ETG is the proportion of people living with active epilepsy who do not receive appropriate, comprehensive treatment from among the total number of people living with active epilepsy in a population [2]. The prevalence of a primary ETG, defined as the proportion of people with active epilepsy not currently receiving any anti-seizure medications (ASMs), is high in low- and middle-income countries. Conversely, an advanced ETG, defined as the proportion of individuals with active epilepsy not receiving specialised care when required, is an issue in high-income countries [1]. Speciality care is defined as referral to a neurologist or epilepsy specialist for further diagnostic workup and seizure classification, including evaluations to exclude other paroxysmal neurologic or psychogenic syndromes that resemble epilepsy. The primary problem associated with an advanced ETG is the prolonged period without the necessary specialised care. To improve the care for patients with epilepsy, the American Academy of Neurology (AAN) established standardized quality measures in 2009 [3]. In the 2017 revision, the work group prioritized the development of measures that address four key areas: (1) counselling for women with childbearing potential, (2) referral or discussion of referral to a comprehensive epilepsy care centre for patients with intractable (treatment-resistant) epilepsy, (3) quality-of-life (QOL) outcome assessments, and (4) depression and anxiety screening [4]. These quality measures could serve as a guideline to avoid an advanced ETG.

Since the implementation of a free-access system for primary care and a universal national medical insurance system in Japan in 1961, almost all patients with epilepsy requiring treatment have received it, resulting in a low primary ETG. However, Japan's medical care system

* Corresponding author at: Department of Pediatrics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan.
*E-mail address:* fukuyama@shinshu-u.ac.jp (T. Fukuyama).

https://doi.org/10.1016/j.ebr.2023.100628
Received 7 August 2023; Received in revised form 26 September 2023; Accepted 15 October 2023
Available online 16 October 2023

for epilepsy faces a shortage of epileptologists in relation to the number of patients, leading to numerous patients being treated only by non-specialist physicians. According to the National Database Open Data, the rate of administration of epilepsy surgery in patients with drug-resistant epilepsy in Japan is approximately half of that in the United States [5,6]. To better address the insufficient epilepsy care, Japan's Ministry of Health, Labour and Welfare launched an epilepsy regional medical cooperation project in 2016. Nevertheless, the causes of the insufficient epilepsy care in Japan are yet to be investigated.

Herein, we retrospectively evaluated patients visiting a newly established epilepsy division to investigate the quality of epilepsy care in a region in Japan without prior specialised epilepsy care, according to the AAN's epilepsy quality measures, and to identify the causes and characteristics of the limited epilepsy care in Japan.

## Materials and methods

### *Geographical and institute characteristics*

In April 2018, we established a new epilepsy division at Shinshu University Hospital and a satellite outpatient division at Nagano Red Cross Hospital. Shinshu University Hospital is in a city with a population of 240,000 at the centre of Nagano Prefecture. The Nagano Red Cross Hospital is in the most populous city (370,000 people) in the northern part of the prefecture. Nagano Prefecture (total population: approximately 2 million) is located approximately in the centre of the Japanese archipelago. Prior to the establishment of our epilepsy division, patients with epilepsy residing in Nagano Prefecture had to travel by public transportation for >2 hours to visit comprehensive epilepsy centres in other prefectures.

The new epilepsy division comprises epileptologists, paediatric neurologists, neurologists, neurosurgeons, and various allied medical professionals. The division offers a range of diagnostic services, including video-electroencephalography (EEG) monitoring, magnetic resonance imaging (MRI), positron emission tomography, and genetic testing for epilepsy. Prior to the establishment of the epilepsy division, video-EEG monitoring was available only at a Children's Hospital in the region. We commenced epilepsy surgery in 2021. Moreover, various departments and divisions, including the Department of Psychiatry, Centre for Gene Medicine and Research, Department of Clinical Laboratory Medicine, Department of Radiology, Department of Pharmacy, and the Medical Welfare Center, have collaborated to provide comprehensive epilepsy care.

### *Patients and study design*

We conducted a retrospective analysis of patients who first visited our new epilepsy division, including the satellite outpatient division, between April 2018 and March 2021. We analyzed patients who had been treated with ASMs for a minimum of 1 year and lived in Nagano Prefecture. Patients who were not treated with ASMs, treated with ASMs for less than a year, or previously lived in another prefecture were excluded. We divided them into two distinct groups: (1) patients who had ongoing seizures or seizure-mimicking episodes despite receiving epilepsy treatment (seizure-persist group) and (2) those who had not experienced seizures or seizure-mimicking episodes for over a year before visiting our epilepsy division (seizure-free group). For each group, we analysed the following patient characteristics separately for adults and children (<16 years old): age at onset of symptoms, age at the first visit to the epilepsy division, duration from onset to visit, purpose of visit, presence of suspected drug-resistant epilepsy (DRE), whether the referring physician was an epileptologist, experience of visiting comprehensive epilepsy centres in other prefectures, and diagnosis (including epilepsy syndrome). Suspected DRE was defined as a failure to achieve seizure freedom, despite at least two ASMs for > year, according to the consensus proposal of the International League Against Epilepsy (ILAE) Commission task force [7]. An epileptologist was defined as a physician certified by the Japanese Epilepsy Society. The diagnosis in all patients was made by our epileptologists based on the ILAE Commission task force 2017 and 2022 classifications of epilepsy which included epilepsy types, syndromes, and aetiology classification [8–10].

In accordance with the AAN's epilepsy quality measures in 2017, we defined patients with advanced ETG as those who could achieve a favourable outcome in terms of their seizures, prepare for pregnancy, and improve their QOL after specialized epilepsy care. In practice, we assessed the effectiveness of therapeutic interventions 30 months after the patient's initial visit to our epilepsy division, and the effectiveness of the interventions were classified as follows for each patient. 1) improved seizures with ASM management; 2) improved seizures with surgery; 3) successfully withdrew ASMs without seizure recurrence; 4) mitigated the side effects of ASMs without seizure aggravation; 5) changed or reduced ASMs with teratogenic potential prior to pregnancy; and 6) lack of a favourable outcome with no significant improvement observed. An improved seizure outcome was defined as a reduction in seizure frequency exceeding 50 %. Patients who achieved outcomes 1) to 5) under our care were considered to have had an advanced ETG in this study. Because the side effects of ASMs were reported to be the most important negative factor affecting QOL of patients with epilepsy [11], this measure was included.

This study was approved by the clinical research review committee of the Shinshu University Ethics Committee (approval number: 5505). Patient consent was obtained using an opt-out method.

## Results

A total of 381 patients visited our epilepsy division, 303 and 78 of whom were treated at Shinshu University Hospital and Nagano Red Cross Hospital, respectively. Initially, 144 patients visited within the first year of the establishment of the epilepsy division, 120 within the second year, and 117 within the third year. Of these patients, 231 met the inclusion criteria. Of the 150 excluded patients, 100 had not been treated with ASMs, 40 had been treated with ASMs for less than a year, and 10 had previously lived in another prefecture. Of the 381 patients, 379 were Japanese, 1 was Chinese, and 1 was Filipino. The seizure-persist group included 169 patients, and the seizure-free group included 62 patients.

### *Patient characteristics*

Table 1 summarises the characteristics of the patients in the seizure-persist and seizure-free groups. The data were categorised according to age, distinguishing between children and adults. Notably, within the seizure-free group, female patients were predominant among both children and adults. For adult patients, the median age at the time of the first visit to the epilepsy division was 32 years for the seizure-persist group and 22.5 years for the seizure-free group, while for children, the respective median ages were almost the same in both groups. The proportion of adult patients with childhood-onset (onset age <16 years) epilepsy was 62.9 % in the seizure-persist group and 74.0 % in the seizure-free group. The proportion of patients with suspected DRE was 61.5 % among children and 82.5 % among adults in the seizure-persist group. None of the referring physicians was an epileptologist for the paediatric patients, while the proportion of epileptologists among the referring physicians for adults was approximately 10 % in both the seizure-persist and seizure-free groups. Patients with previous attendance at a comprehensive epilepsy centre in other prefectures prior to a visit to our epilepsy division accounted for 15.4 % and 30.8 % in children and adults of the seizure-persist group, respectively. This proportion in the patients with suspected DRE was 18.8 % and 34.7 %, respectively.

**Table 1**
Patient characteristics.

| | Seizure-persist groupN (%) or median (range) | | Seizure-free groupN (%) or median (range) | |
|---|---|---|---|---|
| | Children (N = 26) | Adults (N = 143) | Children (N = 12) | Adults (N = 50) |
| Female(s) | 13 (50 %) | 76 (53.1 %) | 8 (66.7 %) | 37 (74.0 %) |
| Median age at the time of the visit to the epilepsy division (range) (years) | 10.5 (5–15) | 32 (0–81) | 11.5 (0–15) | 22.5 (0–72) |
| Median age at the onset (range) (years) | 6 (0–13) | 14 (0–70) | 5 (0–11) | 10.5 (0–71) |
| Onset age <16 years | 26 (100 %) | 90 (62.9 %) | 16 (100 %) | 37 (74.0 %) |
| Suspected drug-resistant epilepsy | 16 (61.5 %) | 118 (82.5 %) | – | – |
| Referring physician was an epileptologist | 0 (0 %) | 15 (10.5 %) | 0 (0 %) | 5 (10.0 %) |
| Previous attendance at a comprehensive epilepsy centre in other prefectures | 4 (15.4 %) | 44 (30.8 %) | 0 (0 %) | 10 (20 %) |

*Purpose of the visit to our epilepsy division*

Table 2 presents a summary of the purpose behind the visit to our epilepsy division. Of the children in the seizure-persist group, 69.2 % sought assistance in reducing seizures and episodes that mimicked seizures, while the remainder sought a second opinion regarding epilepsy care. Conversely, of the adults in the seizure-persist group, 77.6 % sought assistance in reducing seizures and seizure-mimicking episodes, 7.7 % sought a second opinion on epilepsy care, and 7.0 % sought transfer from an epilepsy centre in another prefecture while living in Nagano Prefecture.

Most children in the seizure-free group sought consultation regarding the discontinuation of ASMs. Of the adults in the seizure-free group, 36 % sought assistance with transition from paediatric to adult care systems, 20 % sought counselling for childbearing, and 14 % sought consultation on the cessation of ASMs.

**Table 2**
Purpose of the visit to our epilepsy division.

| | Seizure-persist groupN (%) or median (range) | | Seizure-free groupN (%) or median (range) | |
|---|---|---|---|---|
| | Children (N = 26) | Adults (N = 143) | Children (N = 12) | Adults (N = 50) |
| Second opinion regarding epilepsy care | 8 (30.8) | 11 (7.7 %) | 1 (8.3 %) | 7 (14 %) |
| Assistance in reducing seizures and episodes mimicking seizures | 18 (69.2 %) | 111 (77.6 %) | 0 | 0 |
| Assistance in the transition from the paediatric to the adult care systems | 0 | 5 (3.5 %) | 0 | 18 (36 %) |
| Transfer from an epilepsy centre in another prefecture for residents of the Nagano prefecture) | 0 | 10 (7.0 %) | 0 | 4 (8 %) |
| Consultation regarding the cessation of ASMs | 0 | 0 (0 %) | 11 (91.7 %) | 7 (14 %) |
| Consultation regarding the side effect of ASMs | 0 | 3 (2.1 %) | 0 | 2 (4 %) |
| Counselling for childbearing | 0 | 2 (1.4 %) | 0 | 10 (20 %) |
| Consultation regarding driving license and employment | 0 | 1 (0.7 %) | 0 | 2 (4 %) |

*Diagnosis*

We reviewed the diagnoses of the 231 patients based on their medical history, physical examination, EEG, MRI, and genetic testing results, if any (Table 3). Seventeen patients had both epileptic seizures and non-epileptic episodes, whereas two patients lacked a confirmed diagnosis.

For the children in the seizure-persist group, the diagnoses were

**Table 3**
Diagnosis.

| | N | Seizure-persist group | | Seizure-free group | |
|---|---|---|---|---|---|
| | | Children (N = 26) | Adults (N = 143*) | Children (N = 12) | Adults (N = 50) |
| ***Definite focal epilepsy syndromes*** | 30 | 6 (23.1 %) | 15 (10.5 %) | 1 (8.3 %) | 8 (16 %) |
| Mesial temporal epilepsy with hippocampal sclerosis | | 0 | 10 | 0 | 2 |
| Sleep-related hypermotor epilepsy | | 0 | 3 | 0 | 2 |
| Self-limited epilepsy with centro-temporal spikes or autonomic seizures | | 6 | 0 | 1 | 3 |
| Epilepsy with auditory feature | | 0 | 2 | 0 | 1 |
| ***Focal non-syndromic epilepsy*** | 88 | 5 (19.2 %) | 71 (49.7 %) | 0 (0 %) | 12 (24 %) |
| Temporal lobe epilepsy | | 0 | 19 | 0 | 3 |
| Frontal lobe epilepsy | | 1 | 14 | 0 | 2 |
| Parieto-occipital lobe epilepsy | | 0 | 5 | 0 | 0 |
| Multi focal epilepsy | | 2 | 1 | 0 | 0 |
| Epileptic foci with undetermined localisation | | 2 | 32 | 0 | 7 |
| ***Idiopathic generalised epilepsy*** | 46 | 5 (19.2 %) | 15 (10.5 %) | 5 (41.7 %) | 21 (42 %) |
| Juvenile myoclonic epilepsy | | 0 | 8 | 0 | 4 |
| Juvenile absence epilepsy | | 1 | 3 | 0 | 3 |
| Epilepsy with generalised tonic-clonic seizures alone | | 3 | 3 | 3 | 13 |
| Childhood absence epilepsy | | 1 | 1 | 2 | 1 |
| ***Developmental and epileptic encephalopathy*** | 15 | 3 (11.5 %) | 11 (7.7 %) | 1 (8.3 %) | 0 (0 %) |
| Infantile epileptic spasm syndrome | | 1 | 2 | 0 | 0 |
| Lennox-Gastaut syndrome | | 1 | 8 | 0 | 0 |
| Epileptic encephalopathy with spike-wave activation in sleep | | 1 | 1 | 0 | 0 |
| Epilepsy with myoclonic-atonic seizures | | 0 | 0 | 1 | 0 |
| ***Combined generalised and focal epilepsy*** | 7 | 0 (0 %) | 6 (4.2 %) | 0 (0 %) | 1 (2 %) |
| ***Other epilepsy with a genetic aetiology*** | 16 | 1 (3.8 %) | 8 (5.6 %) | 2 (12.5 %) | 5 (10 %) |
| ***Unclassified epilepsy*** | 13 | 4 (15.4 %) | 6 (4.2 %) | 1 (8.3 %) | 2 (4 %) |
| ***Non-epilepsy episode*** | 31 | 7 (26.9 %) | 18 (12.6 %) | 2 (16.7 %) | 4 (8 %) |
| Psychogenic non-epileptic seizures | | 2 | 7 | 1 | 0 |
| Syncope | | 1 | 2 | 0 | 1 |
| Behavioural episode | | 2 | 6 | 0 | 2 |
| Others | | 2 | 3 | 1 | 1 |

*A diagnostic conclusion could not be achieved for two patients.

almost evenly distributed across definite focal epilepsy syndromes, focal non-syndromic epilepsy, idiopathic generalised epilepsy (IGE) and non-epileptic episodes. Conversely, among adults in the seizure-persist group, the most prevalent diagnosis was focal non-syndromic epilepsy. Non-epileptic episodes were identified in seven of 26 children and 18 of 143 adults in the seizure-persist group.

In the seizure-free group, the most common diagnosis in children and adults was IGE. Non-epileptic episodes were identified in two of 12 children and four of 50 adults.

### *Results of therapeutic interventions from our epilepsy division*

We provided therapeutic interventions to 160 patients (30 and 130 patients in the seizure-free and seizure-persist groups, respectively), excluding those who were deemed not to require a change in treatment and those who did not wish to be treated at our epilepsy division.

#### *Seizure-persist group*

Table 4A presents the results of the therapeutic interventions in the seizure-persist group. Thirteen of 19 paediatric patients and 96 of 111 adult patients fulfilled the criteria for suspected DRE.

Of the 13 paediatric patients, nine (47 %) experienced improved seizure control with ASM management, with medication changes in five and dosage adjustments in four patients. Among these, six achieved seizure freedom; five achieved immediate seizure freedom with our treatment plan at their initial visit, and the other obtained seizure freedom in the second plan. Two children experienced seizure improvement with resective surgery; both had focal epilepsy following acute encephalopathy. Additionally, one patient with Lennox-Gastaut syndrome achieved seizure improvement with vagus nerve stimulation. In four patients, ASMs were successfully withdrawn without seizure recurrence; their diagnose were self-limited epilepsy and non-epileptic episodes in two patients and non-epileptic episodes only in two patients.

Among the adult patients, 54 experienced improved seizure control with ASM management, with medication changes in 45, dosage adjustments in eight, and improved adherence in one patient. Among these, 25 achieved seizure freedom; 19 achieved seizure freedom with a treatment plan at their initial visit, while the remainder obtained seizure freedom in the second and subsequent plans. A patient diagnosed with hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome showed improvement in his condition following treatment tailored to the underlying aetiology [12]. Among the 17 adult patients whose seizure control improved with surgery, 15 underwent resective surgery, while the remaining two underwent callosotomy and vagus nerve stimulation. Among the 10 patients who achieved seizure freedom with resective surgery, eight were diagnosed with mesial temporal epilepsy with hippocampal sclerosis, while the remaining two had tumour-related epilepsy and focal cortical dysplasia of the temporal lobe. Eight of the 10 patients with seizure freedom underwent surgery within one year from their initial visit. Of the five patients whose seizures improved but did not reach seizure freedom with resective surgery, three had frontal lobe epilepsy (including one patient with a frontal encephalocele and epilepsy [13]), one had mesial temporal epilepsy with hippocampal sclerosis and one had occipital epilepsy. The median age at the time of surgery for the treated patents was 50 years (range 17–73 years), with a median period from seizure onset to surgery of 18 years (range, 1–50 years). In 11 adult patients, ASMs were successfully withdrawn without seizure recurrence, including one patient with juvenile myoclonic epilepsy and non-epileptic episodes, one patient with childhood absence epilepsy and non-epileptic episodes, and nine patients with non-epileptic episodes alone. Additionally, the concerns regarding the ASM side effects (aggression in two patients, depression in one patient, and dizziness in one patient) were effectively addressed in four patients.

**Table 4**
Results of therapeutic interventions from our epilepsy division.

*A. Seizure-persist group*

| | Children (N = 19) | Adults (N = 111) |
|---|---|---|
| Improved seizures with ASM management | 9 (47.4 %) | 54 (48.6 %) |
| Improved seizures with surgery | 3 (15.8 %) | 17 (15.3 %) |
| Withdrew ASMs | 4 (21.1 %) | 11 (9.9 %) |
| Mitigated the side effects of ASMs | 0 (0 %) | 3 (2.7 %) |
| Lack of a favourable outcome | 3 (15.8 %) | 26 (23.4 %) |

*B. Seizure-free group*

| | Children (N = 9) | Adults (N = 21) |
|---|---|---|
| Withdrew ASMs | 6 (66.7%) | 6 (28.6%) |
| Mitigated the side effects of ASMs | 0 (0%) | 4 (19.0%) |
| Changed or reduced ASMs with teratogenic potential | 0 (0%) | 10 (47.6%) |
| Lack of a favourable outcome | 3 (33.3%) | 1 (4.8%) |

ASM, anti-seizure medication.

#### *Seizure-free group*

Table 4B presents the results of the therapeutic interventions in the seizure-free group. Among the children, six of the 11 patients who sought consultation for the cessation of ASMs were able to withdraw their ASMs without seizure recurrence. The diagnoses were childhood absence epilepsy in two patients, non-epileptic episodes in two, self-limited epilepsy with autonomic features in one, and genetic epilepsy with febrile seizures plus in one.

Among the adult patients, 10 had either changed or reduced ASMs with teratogenic potential prior to pregnancy, where the purpose of the visit was counselling for childbearing in six patients, assistance in transition from paediatric to adult care systems in three, and transfer from an epilepsy centre in another prefecture while living in the Nagano Prefecture in one. In six patients, ASMs were withdrawn without seizure recurrence. The diagnoses were self-limited epilepsy/childhood absence epilepsy and non-epileptic episodes in three patients, self-limited epilepsy with an abnormal EEG in one and non-epileptic episodes in one. In four patients, their concerns regarding the ASM side effects (sleepiness in two, depression in one, and dizziness in one) were resolved.

### *Changes in the proportion of patients with an advanced ETG among all patients who visited our epilepsy division since its establishment*

Fig. 1 illustrates the proportions of the results of our therapeutic interventions among all patients who visited our epilepsy division in the first, second and third years since its establishment. In the first year, the proportion of patients with an advanced ETG was 45.8 %, which decreased to 28.3 % in the second year and further to 23.1 % in the third year. Among them, the proportion of patients with improved seizure control with ASM management and those who withdrew ASMs was obviously higher in the first year than in the second and third years. As the proportion of patients with an advanced ETG decreased, the proportion of patients who did not meet the inclusion criteria of this study (i.e., patients who were not treated with ASMs or treated with ASMs for less than a year) increased from 28.5 % in the first year, to 42.5 % in the second year, and to 49.6 % in the third year.

## Discussion

In this study, we investigated the characteristics of patients who visited a newly established epilepsy division to evaluate the quality of epilepsy care in a region in Japan that previously lacked specialised epilepsy care. Of the 169 patients in the seizure-persist group, 83 had not received specialised care for seizure reduction (63 required ASM management and 20 required surgery), 15 had been treated with ASMs owing to misdiagnosis, and seven had experienced side effects from

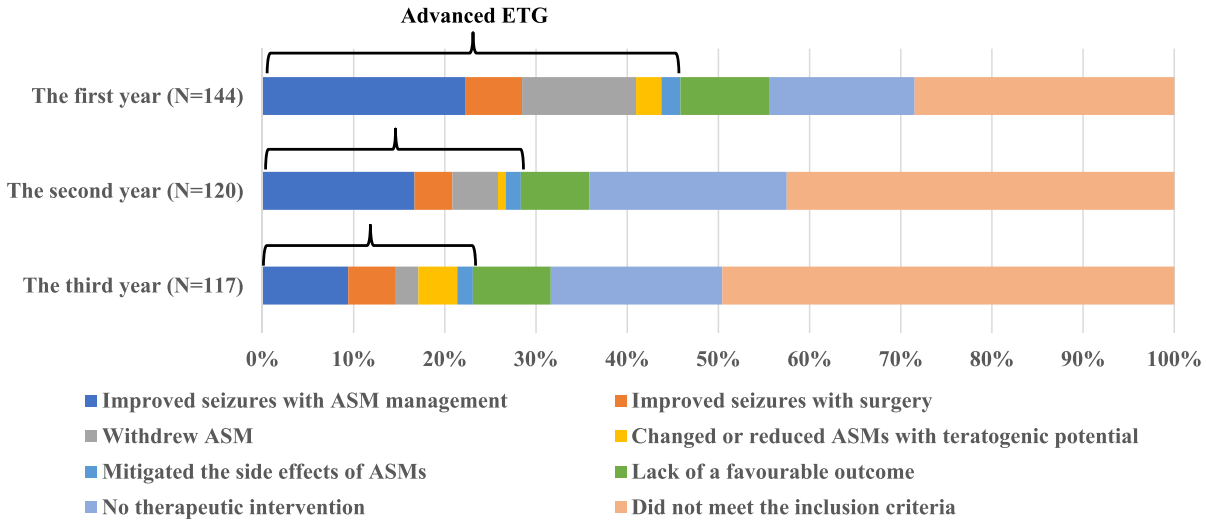


**Fig. 1.** Changes in the proportions of patients with an advanced epilepsy treatment gap (ETG) among all the patients who initially visited our epilepsy division since its establishment.

ASMs. Among the 62 patients in the seizure-free group, 12 had been treated with unnecessary ASMs, 10 women with childbearing potential had been treated with avoidable ASMs with teratogenic potential and four had experienced side effects of ASMs. These patients were classified as having an advanced ETG because they had not previously received the necessary specialised care for more than a year before visiting our epilepsy division. The progressive decline in the number of patients with advanced ETGs following the establishment of our epilepsy division suggests there was a long-standing accumulation of such patients in this region, and the establishment of our epilepsy division has gradually addressed this issue. Our study thus contributes to the revelation of the inadequacies in epilepsy care and demonstrates the positive impact of establishing an epilepsy division in a region of Japan. This underscores the validity of implementing the epilepsy regional medical cooperation project initiated by the Ministry of Health, Labour and Welfare of Japan.

The standardised epilepsy quality measures established by the American Academy of Neurology recommend referral or discussion of referral to a comprehensive epilepsy care centre for patients with intractable epilepsy on an annual basis [4]. In this study, among the patients in the seizure-persist group, only 28.4 % (48/169) had an experience of visiting a comprehensive epilepsy centre in other prefectures. Moreover, this proportion was only 32.8 % (44/134) even among patients with suspected DRE, which is a referral criterion to a comprehensive epilepsy centre according to ILAE [7]. Our patients with an advanced ETG included cases of 'pseudo-drug-resistant epilepsy', which may arise owing to misdiagnosis of epilepsy or seizure type, incorrect choice of ASMs, incorrect dosage, or poor adherence [14], as well as epilepsy cases that required surgical interventions. Moreover, 18.9 % (32/164; 24 with ASMs management, 8 with surgical interventions) immediately achieved freedom from seizures by visiting the epilepsy division. The presence of these patients indicates that the referral criteria are not sufficiently useful or that there may be obstacles in the referral process. Previous studies investigating the causes of delays in epilepsy surgery primarily attributed them to physicians' reluctance to initiate referrals and to discrepancies in the opinions regarding epilepsy surgery between epilepsy experts and general neurologists [15–17]. However, this study suggests that establishing facilities that provide accessible specialised care prompted a flow of referral of patients to improved care. In fact, the availability of specialised epilepsy care in the United States improved with the establishment of the National Association of Epilepsy Centers and an increased number of epilepsy centres [18,19]. Thus, an inadequate supply of specialised epilepsy facilities may be the simple cause of an advanced ETG.

The presence of patients with an advanced ETG in the seizure-free group is also a significant finding in this study. Although most patients in whom ASMs could be successfully withdrawn were those with childhood absence epilepsy or self-limited epilepsy, their previous physician refrained from withdrawing ASMs. Particularly in adult patients, non-epileptic episodes or EEG abnormalities were the reason for maintaining long-term ASM use initially prescribed in childhood. Because of the potential risk of seizure recurrence by withdrawal of ASMs, diagnostic workup is required, including measures such as precise seizure classification and determination of the epileptic syndrome, as well as evaluation to exclude non-epileptic episodes. Additionally, specialised care for epilepsy is necessary for women preparing for pregnancy and for managing the side effects of ASMs. Therefore, the decision to reduce or switch to alternative ASMs must be based on an accurate diagnosis. Even for patients who are seizure-free, it is crucial to establish a streamlined referral system to access specialised care pertaining to the withdrawal of ASMs, preparation for pregnancy, and resolution of ASM side effects.

The large number of patients with childhood-onset epilepsy was one of the features of this study. The transition from paediatric to adult care is challenging in childhood-onset epilepsy, with issues such as a lack of knowledge among adult neurologists, complexities of treatment and complications, self-management, and attachment between paediatricians and families [20–22]. One of the published recommendations for epilepsy transitions from paediatric to adult care [23] emphasised the importance of reevaluating the epilepsy diagnosis to optimise treatment in adolescent patients with persistent seizures. Our study indicates several patients with an advanced ETG accumulated in the absence of a proper re-evaluation system. Re-evaluation of the epilepsy diagnosis and provision of care by specialists, not only in seizure-persistent adolescent patients, but also in seizure-free adolescent patients, is mandatory to reduce an advanced ETG during the period of transition.

This study had several limitations. First, owing to its retrospective design, we were unable to estimate the proportion of patients with an advanced ETG in the regional population. Second, as we did not perform a comparative study with other epilepsy centres and other regions in Japan where there is still no epilepsy centre established, our ability to evaluate the influence of a specialised epilepsy division on patients with an advanced ETG may be restricted. Finally, we could not study QOL and psychiatric/psychological impacts by going to a specialized epilepsy care division, which is an important part of AAN's epilepsy care quality measures. Nonetheless, this study highlights the fact that a significant number of patients with advanced ETG exist in Japan and await proper

countermeasures.

## Conclusion

Numerous patients with an advanced ETG visited our new epilepsy division and our interventions contributed to reducing these gaps. We have clarified this by using AAN's quality criteria for epilepsy care standard. As of August 2023, designated epilepsy care institutions including our new epilepsy division have been established in 28 prefectures through the efforts of the epilepsy regional medical cooperation project by Japan's Ministry of Health, Labour and Welfare. Our study indicates the significance of this project in improving the quality of epilepsy care in Japan.

## Ethical statement

This study was approved by the clinical research review committee of the Shinshu University Ethics Committee (approval number: 5505). Patient consent was obtained using an opt-out method.

## Funding

This work was supported by a Health and Labor Sciences Research Grant on rare and intractable diseases from the Ministry of Health, Labor and Welfare, Japan (Grant No JPMH20FC1039).

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

## References

[1] Kwon C-S, Wagner RG, Carpio A, Jetté N, Newton CR, Thurman DJ. The worldwide epilepsy treatment gap: a systematic review and recommendations for revised definitions - a report from the ILAE epidemiology commission. Epilepsia 2022;63:551–64. https://doi.org/10.1111/epi.17112.

[2] Meinardi H, Scott RA, Reis R, Sander JW. ILAE commission on the developing world. the treatment gap in epilepsy: the current situation and ways forward. Epilepsia 2001;42:136–49. https://doi.org/10.1046/j.1528-1157.2001.32800.x.

[3] Fountain NB, Van Ness PC, Swain-Eng R, Tonn S, Bever Jr CT. American academy of neurology epilepsy measure development panel and the American medical association-convened physician consortium for performance improvement independent measure development process. Quality improvement in neurology: AAN epilepsy quality measures: report of the quality measurement and reporting subcommittee of the American academy of neurology. Neurology 2011;76:94–9. https://doi.org/10.1212/WNL.0b013e318203e9d1.

[4] Patel AD, Baca C, Franklin G, Herman ST, Hughes I, Meunier L, et al. Quality improvement in neurology: epilepsy Quality Measurement Set 2017 update. Neurology 2018;91(18):829–36.

[5] Iwasaki M, Saito T, Tsubota A, Murata T, Fukuoka Y, Jin K. Budget impact analysis of treatment flow optimization in epilepsy patients: estimating potential impacts with increased referral rate to specialized care. J Health Econ Outcomes Res 2021;8:80–7. https://doi.org/10.36469/jheor.2021.24061.

[6] Kaiboriboon K, Malkhachroum AM, Zrik A, Daif A, Schiltz NM, Labiner DM, et al. Epilepsy surgery in the United States: analysis of data from the national association of epilepsy centers. Epilepsy Res 2015;116:105–9.

[7] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51(6):1069–77.

[8] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21. https://doi.org/10.1111/epi.13709.

[9] Riney K, Bogacz A, Somerville E, Hirsch E, Nabbout R, Scheffer IE, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE task force on nosology and definitions. Epilepsia 2022;63(6):1443–74.

[10] Wirrell EC, Nabbout R, Scheffer IE, Alsaadi T, Bogacz A, French JA, et al. Methodology for classification and definition of epilepsy syndromes with list of syndromes: report of the ILAE task force on nosology and definitions. Epilepsia 2022;63(6):1333–48.

[11] Gilliam F. Optimizing health outcomes in active epilepsy. Neurology 2002;58:S9–. https://doi.org/10.1212/wnl.58.8_suppl_5.s9.

[12] Hoshino Y, Kodaira M, Matsuno A, Kaneko T, Fukuyama T, Takano K, et al. Reversible Leukoencephalopathy in a Man with childhood-onset hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Intern Med 2022;61(4):553–7.

[13] Yamazaki K, Kanaya K, Uda T, Fukuyama T, Nishioka M, Hoshino Y, et al. Frontal encephalocele plus epilepsy: A case report and review of the literature. Brain Sci 2023:13. https://doi.org/10.3390/brainsci13010115.

[14] Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med 2011;365:919–26. https://doi.org/10.1056/NEJMra1004418.

[15] Erba G, Moja L, Beghi E, Messina P, Pupillo E. Barriers toward epilepsy surgery. A survey among practicing neurologists. Epilepsia 2012;53:35–43. https://doi.org/10.1111/j.1528-1167.2011.03282.x.

[16] Casciato S, Morano A, Ricci L, Asioli S, Barba C, Caulo M, et al. Knowledge and attitudes of neurologists toward epilepsy surgery: an Italian survey. Neurol Sci 2022;43(7):4453–61.

[17] Alexandre V, Capovilla G, Fattore C, Franco V, Gambardella A, Guerrini R, et al. Characteristics of a large population of patients with refractory epilepsy attending tertiary referral centers in Italy. Epilepsia 2010;51(5):921–5.

[18] Labiner DM. Accreditation of epilepsy centers. Epilepsy Curr 2021;21:132–3. https://doi.org/10.1177/1535759721991568.

[19] Ostendorf AP, Ahrens SM, Lado FA, Arnold ST, Bai S, Bensalem Owen MK, et al. United States epilepsy center characteristics: a data analysis from the national association of epilepsy centers. Neurology 2022;98(5):e449–58.

[20] Borlot F, Tellez-Zenteno JF, Allen A, Ali A, Snead 3rd OC, Andrade DM. Epilepsy transition: challenges of caring for adults with childhood-onset seizures. Epilepsia 2014;55:1659–66. https://doi.org/10.1111/epi.12752.

[21] Nabbout R, Teng T, Chemaly N, Breuillard D, Kuchenbuch M. Transition of patients with childhood onset epilepsy: perspectives from pediatric and adult neurologists. Epilepsy Behav 2020;104:106889. https://doi.org/10.1016/j.yebeh.2019.106889.

[22] Oguni H, Ito S, Nishikawa A, Otani Y, Nagata S. Transition from pediatric to adult care in a Japanese cohort of childhood-onset epilepsy: prevalence of epileptic syndromes and complexity in the transition. Seizure 2021;88:1–6. https://doi.org/10.1016/j.seizure.2021.03.017.

[23] Andrade DM, Bassett AS, Bercovici E, Borlot F, Bui E, Camfield P, et al. Epilepsy: transition from pediatric to adult care. recommendations of the ontario epilepsy implementation task force. Epilepsia 2017;58(9):1502–17.