Success rate of anti-seizure medication discontinuation in children with epilepsy

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Keywords

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Abstract

Objectives. Epilepsy is a common condition in childhood. Anti-seizure medication (ASM) discontinuation can be considered after two years seizure-freedom. Predictive factors for the success of this withdrawal are needed to simplify the decision-making.

Methods. A literature search was performed to examine the most frequently used predictive variables for risk of recurrence. These 22 variables were then used in a retrospective data search and analysis of 3626 patient files. We focused on those patients seen in 2021 in the epilepsy clinic of the University Hospital of Leuven.

Results. 94 patients between 6 months and 18 years on monotherapy of ASM were included. 21% relapsed after a median of 4 months. Later age at onset of epilepsy, later age at discontinuation and male gender showed a significant effect on the risk of recurrence.

Interpretation. Relapse rate was similar as in existing literature with recurrence occurring more frequently in the first 6 months after discontinuation. Long-lasting epilepsies relapse more frequently. Epilepsy severity, cause and onset are other determinants of recurrence in literature. They were not statistically significant in this study. Further larger prospective studies are needed.

Introduction

Epilepsy is a common chronic neurological condition in childhood (1-4). In Belgium up to 0.4% of the children under the age of 18 years are affected (5). During life this prevalence increases up to 1% (2). Anti-seizure medication (ASM) is the main treatment option to control seizures. Around 70% of the patients with epilepsy achieve seizure freedom with ASM. (2-4,6-11) Many childhood epilepsy syndromes are self-limiting. Considering this, ASM discontinuation can be considered after a seizure-free period of 2 years to minimize the possible adverse effects of long term medication use (2,6,7,9,10,12,13). The complexity of the balance between benefits and risks of this discontinuation should always be carefully considered (1,2,6,7,11,14-18). Neurologists need to take account of multiple factors such as: epilepsy etiology, epilepsy syndrome, quality of life, (long term) negative side effects of the medication, the psychosocial and the economic/financial burden, the risk of recurrence, but also individual preferences (2-4,9-11,15-17). After a careful assessment before ASM discontinuation, 60-90% of the children who stop their medication remit with the highest risk of recurrence in the first 6 to 12 months after withdrawal (1,6,10,13,15,17). Several studies already attempted to determine the best timing and duration of withdrawal. As a general rule, ASM discontinuation is only begun after two-year seizure freedom, although some propose to consider earlier withdrawal in benign childhood epileptic syndromes (1,6,10,13,15,17). Some of them searched for predictive factors for success of withdrawal, such as epilepsy syndrome, cause of epilepsy, seizure type, the age at onset of epilepsy and the age at discontinuation of therapy, the gender of the patient, developmental delay, neurological deficit, history of status epilepticus or febrile seizures, length of the seizure-free period after treatment initiation,...(1,2,6,7,11,12,15,16,18-22). Still, unclarity and discussion on this topic remains. This single center study retrospectively examines the success rate of ASM discontinuation and the predictive factors in children with epilepsy who consulted a tertiary hospital in Belgium during 2021.

Materials and methods

Literature search

Data sources and searches

We performed a literature search in the Pubmed database from 2005 till 2020, using combinations of following Mesh Terms: children, anti-epileptic drugs, stop, withdrawal. Titles and abstracts of 481 articles were examined. We only included articles written in English, French or Dutch that investigated a pediatric non-oncological population. We excluded studies without accessible abstract or article, studies not containing withdrawal as one of the main topics and studies only examining withdrawal of ASM after epilepsy surgery. The reference lists of these articles were scanned for missing studies. 21 articles were withheld, of which 20 contained several predictive factors on risk of recurrence.

Outcome collection

We extracted the most frequently used predictive variables for risk of recurrence from the identified articles.

Data collection and analysis

In this single center study, we investigated the success rate of ASM discontinuation in children with epilepsy between the age of 6 months and 18 years, seen in the epilepsy unit in 2021. The medical records were gathered in the University Hospital of Leuven, a tertiary hospital in Belgium. As a secondary outcome, we examined which variables could be predictive of this success.

Medical records of 3626 patients were retrospectively reviewed and 94 patients, seen in the epilepsy clinic in 2021, could be included using the in- and exclusion criteria mentioned in table 1.

At 6 months post discontinuation and at the end of the follow up (last date July 1 2022), success of discontinuation was assessed.

The 24 predictive variables determined from the literature search were extracted from the medical records. Seizures were classified according to the classification of the international league against epilepsy (ILAE).

The patients were asked only to reconsult if relapsed. We assumed a good adherence to this question and marked the patients as in remission when they did not reconsult. Consultations in other hospitals were examined via the electronical medical record used by this university hospital and several other clinics in Flandres and via the eHealth Hub.

This study received the approval of the Ethische Commissie Onderzoek UZ/KU Leuven.

Table 1: In- and exclusion criteria for data collection.

Inclusion criteria	Exclusion criteria
Outpatient clinic/EEG lab in 2021	Undergone epilepsy surgery
Age between 6 months and 18 years • Older than 6 months at diagnosis • Younger than 18 years at ASM discontinuation	Oncological patients
Seizure free and on monotherapy at time of discontinuation	Follow-up less than 6 months

Statistical analysis

Our retrospective study will consist of a content analysis: we investigate the prevalence of recurrence and analyze the above mentioned predictive variables per patient. We examine how each predictive variable influences the risk of recurrence. The primary outcome is the risk of recurrence, which is a dichotomous variable. The secondary outcomes, the predictive factors, are partly categorical variables and partly continuous variables. In general the categorical variables are dichotomous (e.g. boy/girl) but we also examine some nominal variables like the epilepsy type and the epilepsy syndrome. We compared the data of those who relapse with the data of all the patients included in the study. When categorical variables Chi-Square statistics were used and when continuous variables a Mann Whitney U test.

Results

Literature search

We found 20 articles mentioning predictive factors for discontinuation of anti-seizure medication (ASM). We extracted 23 variables from these articles and counted the number of studies in which they were mentioned. The most elaborated paper on variables was the study of Olmez et al. with 20 variables listed. Tang and Zheng only used two variables on EEG. "Electroencephalography (EEG) pattern at the time of discontinuation" was the most mentioned predictive factor (16 articles), "History of status epilepticus" the least mentioned (2 articles). A variable was on average brought up in 8 articles. Due to low feasibility to extract from medical records, we suppressed "Seizure frequency before entering remission" from our variable list. The 22 variables listed in table 2 were used in further analysis, aware of the risk of overspecification bias caused by the large number of variables.

Data search in medical records

We examined a total of 3626 patient contacts and matching patient files. For the year 2021, 94 patients met the inclusion criteria, 58 boys and 36 girls. Mean age at ASM discontinuation was 9 years (min 1 year, max 17 years). The calculated median time of follow-up was 15 months (min 6 months, max 15 years).

Success rate of ASM discontinuation. Twenty of the 94 included patients re-experienced an epileptic seizure during or after withdrawal of anti-seizure medication. 79% remitted. The median time to relapse was 4 months. At a follow-up of 6 months 12 patients had relapsed. Thus, 60% (12/20) relapsed in the first 6 months after ASM discontinuation. At one year of follow-up this number increased up to 75% (15/20) (see figure 1).

In these 94 patients we examined which of the 22 predictive factors from our literature study were applicable in our small study population. The following factors showed significant differences between those who relapsed and those who did not: age at onset of epilepsy, age at discontinuation of ASM and gender.

Significant difference in age at onset of epilepsy. The median age at onset of the whole group was 4.6 years. In the analysis at last follow-up, the median epilepsy onset age of those with relapse is significantly higher (6.7 years old (p=0,04)). The median age of those with relapse was even higher in the analysis at follow-up of 6 months (7.3years (p=0,01)). They who were diagnosed between the age of 6 and 10 years had the highest percentages of recurrence (see figure 2).

Significant difference in patient's age at discontinuation of ASM. There was a nearly equal distribution of patient's age at discontinuation (see figure 3). Patients who re-experienced an epileptic seizure, had a higher median age at discontinuation of ASM than the control group. In the control group the median age was 9 years. At last follow-up the median age of those with recurrence was 12 years (p=0,04), after fixed follow-up of 6 months it was 13 years (p=0,03). Patients who stopped their medication when older than 9 years had the highest risk of recurrence (see figure 4).

Significant difference in gender. 36 of the included patients were girls (38%). Only 4 of these girls relapsed (11%), one before 6 months after discontinuation of ASM. 16 of the 58 boys had a recurrence of epilepsy (28%), 11 at a follow-up of 6 months. This difference between relapse in genders was significant, but only after a follow-up of six months (at last follow-up: p=0,06; 6 months follow-up: p=0,02).

No significant difference was found for the following predictive variables, although for some variables a trend was seen: epileptic syndrome, seizure type, developmental delay, history of status epilepticus, history of febrile seizures, duration of active epilepsy. No trend was seen in the following variables: etiology of epilepsy, neurological deficit, family history of epilepsy, number of seizures before start ASM, time between first epileptic seizures and start ASM, number and type of different anti-epileptic drugs, time to remission after start ASM, number of seizures before remission, length of seizure-free period after treatment initiation

Table 2: The 22 predictive variables used in further data analysis.

Predictive variables			
Epileptic syndrome	Epileptic etiology	Seizure type	Age at onset of epilepsy
Gender	Neurological deficit	Developmental delay	Family history of epilepsy
History of status epilepticus	History of febrile seizures	Number of seizures before start ASM	Time between first epileptic seizure and start ASM
Number of seizures before remission	Time to remission after start ASM	Length of the seizure-free period after treatment initiation	Duration of active epilepsy
Number of different AED taken before discontinuation	Type of AEDs taken at the time of discontinuation	Patient's age at discontinuation	Duration of tapering period
EEG pattern at the time of discontinuation			

Figure 1: Survival curve of patients in remission.

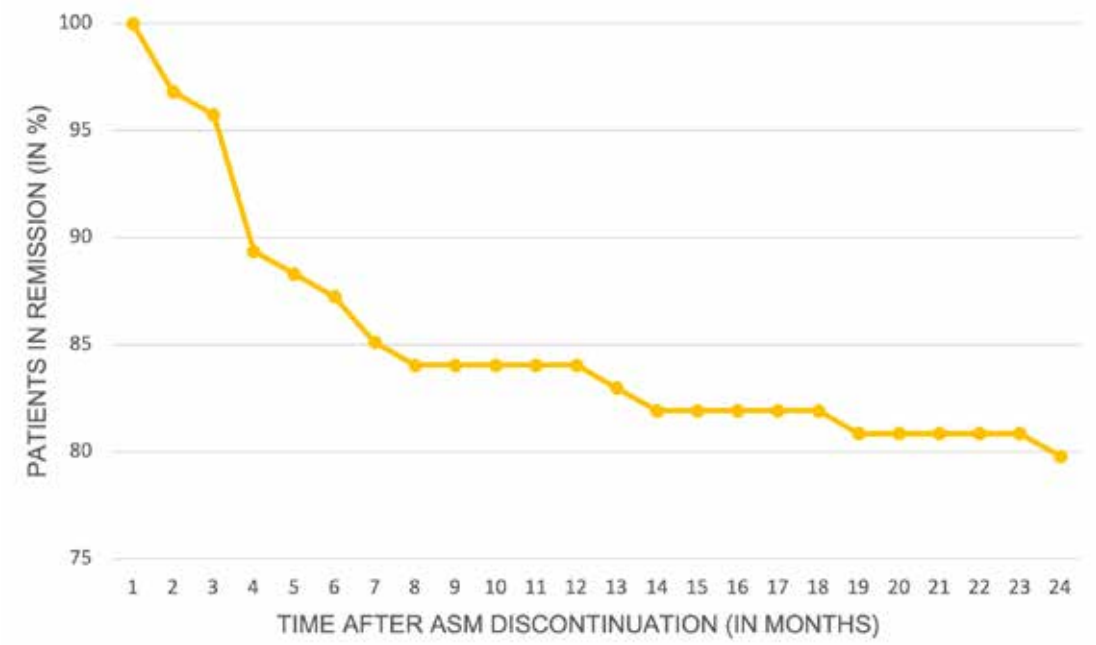
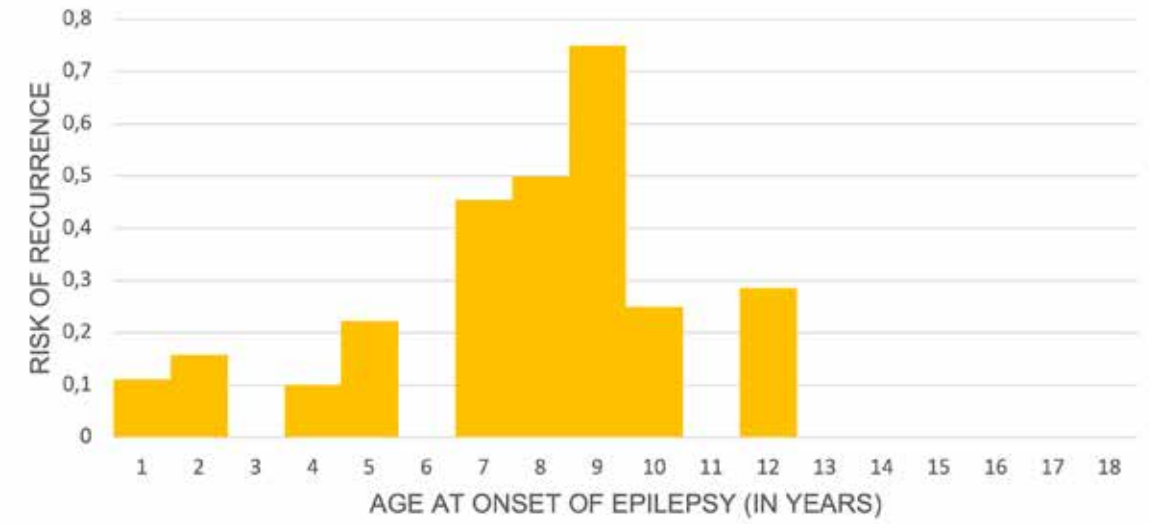


Figure 2: Risk of recurrence as a function of patient's age at onset of epilepsy.



and EEG pattern at the time of discontinuation. In the following sections we will detail some of these findings.

Epileptic syndrome. 57 patients could be classified into an epileptic syndrome/entity. 31 of them had a self-limited epilepsy (e.g. childhood absence epilepsy, childhood epilepsy with centro-temporal spikes, self-limited neonatal convulsions, temporal lobe epilepsy), the other 26 could be classified in West syndrome, epileptic encephalopathy with continuous spike-and-wave during sleep, juvenile myoclonic epilepsy, febrile seizures plus and other (like cerebral palsy). 23% of the patients with a self-limited epilepsy syndrome relapsed at some point, a difference with the 42% failing discontinuations in patients with these less benign epilepsy syndromes. This difference however was not significant (p=0,21). The analysis at 6 months did not show any significant difference either (13% when self-limiting versus 25% when less benign epilepsy syndromes (p=0,34)).

Etiology of epilepsy. The etiology of epilepsy was known in 35 of our study population despite standard diagnostic evaluations. 27 had a structural abnormality and 8 had a genetic cause for epilepsy. We did not notice a significant difference in risk of recurrence.

S*eizure type*. We did not notice a difference in relapse rates between patients with seizures with focal onset and with general onset. When comparing the patients with non-motor onset and motor onset, the first group seems to relapse more frequently than those with motor onset: 27% versus 21%, but this difference was not significant (last follow-up: p=0,63; 6 months follow-up: p=0,98).

Developmental delay. 44% of our included patients had a significant developmental delay. The risk of recurrence was higher in the group with developmental delay: 24% (10 of the 41) versus 19% (10 of the 53), although not significant (at last follow-up: p=0,52; 6 months follow-up: p=0,88).

History of status epilepticus. We did not notice a difference in recurrence between both groups when comparing at last follow-up (p=0,85). At a follow-up of 6 months having a history of status epilepticus seemed to raise the risk of recurrence (12% versus 24%) but this difference was not statistically significant (p=0,89). 22 of the identified patients had a history of status epilepticus.

Figure 3: Number of children per age at ASM discontinuation.

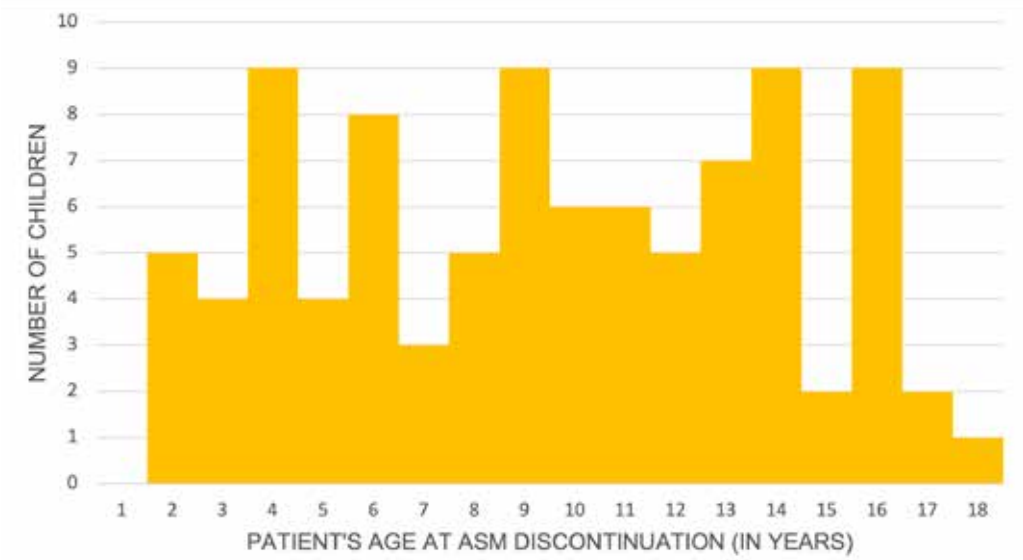
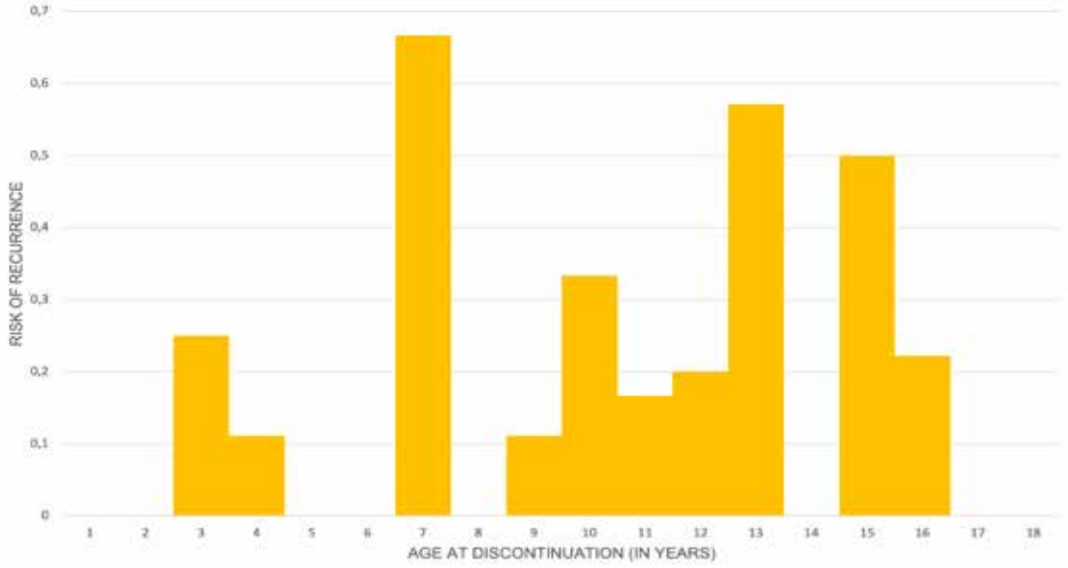


Figure 4: Risk of recurrence as a function of patient's age at ASM discontinuation.



History of febrile seizures. 25 patients had a history of febrile seizures. A trend was seen in the analysis at last follow-up that the overall relapse rate of patients with history of febrile seizures was less (16% vs 23%) than those without history. Statistically this was not significant (p=0,45), neither did the analysis at 6 months after ASM discontinuation find a difference (p=0,89).

Number of seizures before start ASM. The data on this parameter are not complete. In 29 of the 94 included patients the number of seizures before start ASM is not exactly known. This is mostly due to characteristics of the epilepsy syndrome (e.g. absence, ESES) or to unclarity and/or incompleteness in reporting. Of the remaining group of patients, only two patients had more than 5 epileptic seizures before start of medication, 27 patients had only one seizure before start ASM. No difference in risk of recurrence between the different groups was found.

Time between first epileptic seizure and start of anti-seizure medication. In the total group, the median duration of this period was 6 weeks. In those who relapsed at some point and before 6 months after ASM withdrawal, the median duration was 10 (p=0,37) and 12 weeks (p=0,31) respectively.

Time to remission after start ASM. 42 of the identified patients remitted immediately after start ASM. Therefore, 50 patients only used one anti-epileptic drug during the course of epilepsy. Included patients used maximum four anti-epileptic drugs before remission. In both analysis of recurrence at some point and in analysis after a 6 months of follow-up, no significant difference in median time to remission after start ASM was shown (p=0,69 and p=0,95 respectively).

Duration of active epilepsy. The median duration of active epilepsy in the whole group of identified patients was lower (11 months) than of those who ever relapsed (18months), but not significantly so (p=0,31). This difference was even less clear at follow-up of 6 months (p=0,87).

Number of seizures before remission. In 35% of the examined 94 medical records, there were missing data on this topic. The median number of identified seizures before remission is 2 in the whole group and 2,5 in those with recurrence of epilepsy at some point. In those with recurrence before 6 months of follow-up, the median number of identified seizures was 3.

Length of the seizure-free period after treatment initiation. The median duration was 25 months in the 94 included patients. No difference was seen when comparing with those who relapsed (at last follow-up: p=0,84; 6 months follow-up: p=0,62).

Electroencephalogram (EEG) pattern at the time of discontinuation. 43% of the included patients had an EEG before discontinuation of

their ASM. Only 6 of these 40 EEGs (15%) were abnormal. Only one of the 6 patients with abnormal EEG relapsed (after more than 6 months of follow-up). 28 of the 34 patients with an EEG within normal limits remitted. 80% of those without EEG pre-discontinuation remitted. Previous literature also examined the EEG pattern after discontinuation. In this study, only 15 of the 94 included patients had an EEG after discontinuation, of which 6 an abnormal EEG. A high number of those with an EEG performed after discontinuation relapsed (50%).

Table 3: Patient characteristics.

	Relapse	Remission	Sum	p
Number	12	82	94	
Male	11	47	58	
Age at onset of epilepsy (in years)	7,3	4,6		0,01
Age at discontinuation of ASM (in years)	13	9		0,03
Epileptic syndromes				0,34
Self-limited epileptic syndromes	4	27	31	
- Childhood absence epilepsy	2	13	15	
- Childhood epilepsy with centrotemporal spikes	2	8	10	
- Self-limited neonatal seizures	0	1	1	
- Temporal lobe epilepsy	0	6	6	
Other epileptic syndromes, less benign	3	23	26	
- Febrile seizures plus	3	13	16	
- Epileptic encephalopathy with continuous spike-and-wave during sleep	0	3	3	
- Juvenile myoclonic epilepsy	0	3	3	
- West syndrome	0	2	2	
- Other (Cerebral palsy)	0	2	2	
Not classified	5	32	37	
Etiology of epilepsy				
Structural abnormality	4	23	27	
Genetic cause	0	8	8	
Not identified	4	55	59	
Seizure type				
Focal onset	5	40	45	0,59
Generalized onset	7	40	47	
Motor onset	10	66	76	0,98
Non-Motor onset	2	13	15	
Developmental delay	5	36	41	0,88
History of status epilepticus	3	19	22	0,89
History of febrile seizures	3	22	25	0,89
Familial history of epilepsy	1	23	24	0,11

Discussion

94 patients between the age of 6 months and 18 years are included in this study. 21% of these patients relapsed. In literature a recurrence of epileptic seizures of 20-30% is usually reported (1,2,6,9,11,13,15,17,20,21). We conclude that the risk of recurrence in our study is rather low. Given the higher probability of severe epilepsy in a tertiary center, we could have presumed that the risk of recurrence would be higher than usually reported. The lower risk in our study is probably due to multiple factors, such as a pediatric population on monotherapy of ASM, exclusion of patients who have got epileptic surgery and a more conservative approach with a good preselection of candidates to discontinue their ASM.

Literature suggested that recurrence occurred more frequently in the first 6-12 months after ASM discontinuation (1,2,13,18,19). In our study too, the majority of those relapsing, relapsed in that period of time.

That leaves us with the discussion which factors are predictors for recurrence. We choose to examine 22 predictive factors after a literature research. However, this made the risk of overspecification bias larger, especially in combination with the smaller study population.

We identified the following factors which could be associated with a recurrence of epilepsy after ASM discontinuation: age at onset of epilepsy, age at discontinuation of ASM and gender. Gender was only a significant predictive variable at 6 months follow up.

The first two variables are not surprising. Most epilepsy syndromes are age-related (e.g. the most common age to develop childhood absence epilepsy is between 4 and 12 years of age). Etiology and type of epilepsy too are associated with age of onset of the epilepsy (6-9,16,17). Therefore, an older age at onset can reflect certain epileptic syndromes or types of epilepsy which aren't likely to remit. Our study showed a higher risk of recurrence when patients were older at onset and discontinuation (21). Long lasting epilepsies are thus less likely to remit, even after a period of seizure freedom.

Epilepsy syndrome and etiology are crucial factors in determining the severity of epilepsy (6-9,16,17). However in this study population, the difference between relapse of the patients with self-limiting epileptic syndromes and those with less benign epileptic syndromes was not significant (1,2,6,8,10,16,18,19). This is most likely due to the small sample size of our study. Furthermore, 4 of the identified 10 patients with childhood epilepsy with centro-temporal spikes relapse in our study. Given the self-limited characteristic of this epilepsy syndrome, we suggest that the decision of discontinuation was perhaps too early. Median seizure-free period before discontinuation of these patients is 2 years and 2 months. Discontinuation would be successful when performed after a new period of seizure freedom. Two patients with juvenile myoclonic epilepsy were included in this study. Literature suggests that this is generally a lifelong form of epilepsy (1,16,18,19). However, neither of these two patients relapsed after stopping the medication.

Reviewing the current evidence, ASM in epilepsy with either a genetic or an structural cause can almost never be discontinued (6). In our study, we did see some children in these etiological groups without recurrence. In seizures with focal onset, it can be expected that structural anomalities are the leading cause (6,10,21). The existing literature suggests that the rate of recurrence will be higher in focal epilepsy (2,6,7,10,16). This was also not observed in our study.

This retrospective review showed a difference in recurrence of epilepsy in boys and girls at 6 months follow-up. Boys more frequently relapsed in our study, although existing literature described either no difference between genders or a higher risk of relapse in girls (1,2,6,7,13,15,16,20). We do not have a clear explanation for the male predominance in our study.

Afshari et al. described the following factors to affect the rate of recurrence: age at onset of epilepsy, time between first epileptic seizure and start of anti-seizure medication, type and etiology of epilepsy, number of anti-epileptic drugs used before discontinuation, duration of tapering period of ASM and method of the tapering, EEG prior to beginning of therapy discontinuation (6). Beghi et al. states that an abnormal EEG at the time of treatment discontinuation, a documented etiology of seizures, seizures with focal onset and an older age at onset of epilepsy enhanced the risk of relapse (7). The Italian League against Epilepsy adviced to take neither the disease length or severity, nor the number and type of drugs into account (7). Geerts et al. found that age at onset of younger than 6 years, idiopathic epilepsy, absence epilepsy and having a normal EEG were predictive of staying in remission after ASM discontinuation (14). Karalok et al. did not find age at onset of epilepsy nor number of ASM a risk factor (1). Pavlovic et al. found an association of female gender, age at onset of seizures and at withdrawal of ASM, seizure types, EEG worsening during or after ASM withdrawal and age at discontinuation with relapse risk (19).

The study we performed could not confirm most of the findings above. Some of the abovementioned studies included more patients than ours. In some of them also adults were included.

To examine the effects of the parameters of mostly planned ASM discontinuation, only patients on one ASM at discontinuation were included. This inclusion criterion can cause some bias by selecting more benign epileptic syndromes and being not representative for the whole pediatric epileptic population.

In some of the variables there was quite some missing data, either because information was not recorded in the electronical medical record or because tests were not performed. In the clinical site where our study took place, an EEG study was not a standard examination to decide whether or not to discontinue ASM. Unclarity about the predictive value of EEGs still remains (1-3,6-9,13,15-17,19,21). Some studies investigated the effect of an abnormal EEG prior to therapy discontinuation, others the value of an EEG after therapy discontinuation (6,9,13,15,18,19).

Given the characteristics of our studied population, we could not totally exclude a preselection bias (20). We performed a retrospective study with preselection of our subjects by neurologists. The decision to stop or continue medication was not part of a standardized protocol but rather a case by case individual decision. There was not any pre-knowledge of this study. Also, some epilepsy syndromes and other characteristics are underrepresented.

Conclusion

In literature and in clinical practice, major discrepancies to decide on ASM discontinuation in childhood epilepsy remain, with a lack of evidence-based guidelines (18). We found a statistically significant effect of gender, age of epilepsy onset and age at discontinuation on the risk of recurrence. Given the sample size and the preselection bias, no hard conclusions could be made in our study, also not about the effect of epilepsy syndrome on the risk of relapse. Larger prospective studies are needed to further identify the predictive factors.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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