From febrile convulsion to genetic epilepsies

Doctoral (PhD) thesis

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Pécs, 2025

1 Introduction

During my university studies, it gradually became clear to me that I aspired to become a paediatrician, and later, to specialize in paediatric neurology.
The expanding application of molecular genetic testing has made it increasingly possible to identify the genetic backgrounds of numerous epilepsy syndromes. The 2022 classification by the International League Against Epilepsy (ILAE) introduced new categories alongside self-limited epilepsies, including developmental and epileptic encephalopathies, as well as aetiology-specific epilepsies. Among the latter is PCDH19-related epilepsy, a condition that primarily affects females. I set out to collect and analyse data on children diagnosed and treated with PCDH19 epilepsy in Hungary, aiming to contribute to the broader understanding of this rare disorder.

Through my involvement in scientific research as both a medical student and a doctoral candidate, I had the opportunity to participate in epilepsy consultations at the Paediatric Department of the Clinical Centre of the University of Pécs. While childhood absence epilepsy has traditionally been considered a benign condition with a favourable prognosis, advances in neuroimaging and neuropsychological assessment have revealed that affected children may also experience learning difficulties, attention deficits, behavioural problems, and even other seizure types. One of my core research interests has been to critically evaluate whether the long-held assumptions regarding the prognosis of absence epilepsy still hold true considering current evidence.
With the onset of the COVID-19 pandemic in 2020, an increasing number of publications emerged detailing the wide-ranging impacts of the pandemic. In addition to reports on respiratory symptoms, neurological manifestations were also documented in both adults and children. During this period, children were largely excluded from communal environments, which led to a notable decline in the incidence of common infections. However, febrile seizures remained a significant source of concern for caregivers, prompting them to seek emergency medical care even amid widespread restrictions. I sought to investigate whether the incidence of febrile convulsions increased in association with the SARS-CoV-2 pandemic.

2 Objectives, hypotheses

1. To establish a national database of children aged 0–18 years diagnosed with the rare PCDH19-related epilepsy, and to determine the prevalence of the disorder in Hungary. We intended to provide clinical, EEG and brain MRI characteristics of these patients and to identify the most effective antiseizure medication (ASM) strategies used in the management of the condition.
2. We hypothesized there may be a correlation between the clinical manifestations of childhood absence epilepsy, the characteristics of the initial diagnostic EEG, and long-term prognosis. My aim was to investigate whether the choice of the first administered ASM, as well as the total number of ASMs used during treatment, might influence long-term outcomes and the likelihood of relapse. The central question was whether childhood absence epilepsy is truly as benign as previously reported, particularly considering insights gained through modern diagnostic techniques.
3. Investigating convulsions among the neurological manifestations observed during the COVID-19 pandemic, we aimed to assess whether the incidence of febrile seizures changed compared to the pre-pandemic (control) period. We hypothesized that, during the febrile phase of the SARS-CoV-2 pandemic, the number of children under six years of age requiring medical attention for febrile convulsions would increase.

3 PCDH19 epilepsy

3.1 Introduction

PCDH19 epilepsy is characterized by "epilepsy and mental retardation limited to females," the gene pathogenic variant was first described by Dibbens et al. in 2008.[1] To date, only a few hundred patient case reports and multicenter studies are known. The PCDH19 gene pathogenic variant is currently in the ,,top 10" list of epilepsy genes.[2]

3.2 Patients and Methods

At the 2022 congress of the Hungarian Society for Paediatric Neurology, I presented the case of a female patient who was repeatedly hospitalized at the Neurological Ward of the Paediatric Department due to PCDH19-related epilepsy. Motivated by this case, I proposed to fellow paediatric neurologists attending the scientific meeting the creation of a national database to collect and analyse data on Hungarian children diagnosed with PCDH19-related epilepsy. I compiled a questionnaire and distributed it to those paediatric neurologists who indicated that they were following children with confirmed PCDH19 epilepsy. We included patients in whom the pathogenic variant of the PCDH19 gene was confirmed by molecular genetic testing.

We collected in the questionnaire the following data:

- Gender
- Perinatal history (gestational age, birth weight, Apgar score)
- Psychomotor development (motor, speech, intellectual development, autistic traits, sleep disturbances)
- Family history of febrile seizures, epilepsy, or other neurological disorders
- Epilepsy history (age at the time of first seizure and its type, presence of possible provoking factors, frequency of seizures, cluster and/or status epilepticus, time between first and second seizure/cluster)
- Results of first EEG, subsequent changes in EEG findings, and timing of follow-up EEGs
- Brain MRI: age at examination, and presence of structural anomalies
- Exact location and type of the pathogenic PCDH19 gene variant

- Antiseizure medication and its efficacy (duration of therapy, side effects, reasons for discontinuation)
- Current seizure status and length of seizure-free periods

The clinical features, EEG findings, and brain MRI results of patients with genetically confirmed PCDH19 epilepsy were collected using this questionnaire.

3.3 Results

Nine girls with PCDH19-related epilepsy are being followed up by Hungarian paediatric neurologists in seven neuro-paediatric centres.

The nine children had a mean gestational age of 38 weeks (34-40 weeks), a mean birth weight of 2942 grams (2140-3340 grams), and an Apgar score of 9/10. Family history of epilepsy or febrile seizures was reported in five out of nine cases.

The average age of the children at the time of the study was 9.9 years (range: 4.1–24.2 years). The average age at onset of the first seizure was 15 months (range: 5–22 months), with focal onset in 5/9 children and generalized in 4/9. The first seizure occurred in clusters in 7/9 females. The second seizure/cluster appeared after an average of 2.1 months (range: 0–10 months). Seven children developed status epilepticus at least once.

The first EEG examination showed bilateral paroxysmal epileptiform discharges with frontal dominance in six cases. The first EEG of three children showed no abnormalities.

The first brain MRI was performed at an average age of 20 months (range: 5–48 months); abnormalities were detected in 6/9 cases. The following anomalies were found: 1/ left hippocampal sclerosis, 2/ right hippocampal sclerosis, 3/ suspected focal cortical dysplasia and dysgenesis of the left anterior cingulate gyrus. Incidental findings were observed in three cases: ventricular asymmetry, widened extracerebral liquor space, and septum pellucidum cyst/cavum vergae.

Only one girl had age-appropriate intellectual development. Adequate speech development was observed in three cases. *(Table 1)*

Patient No	age at the time of the study (year)	age at the time of first seizure (month)	motor dev.	intellectual dev.	speech dev.	autistic symptoms	sleep dist.	PCDH19 pathogenic variant	Type of mutation
1	4	20	normal	delayed	normal	no	no	*c.1671 C>G (p.Asn557Lys)*	missense
2	5	22	delayed	delayed	delayed	yes	no	*c.208_209insG, p.(His70Argfs*19)*	frameshift
3	24	13	normal	delayed	delayed	yes	-	*c.1019A>G (p.Asn340Ser)*	missense
4	16	6	normal	delayed	normal	yes	no	*c.1022A>G (p.Asp341Gly)*	splicing
5	12	22	normal	delayed	delayed	yes	no	*c.1152_1180del (p.Gln385Serfs*6)*	frameshift
6	11	18	normal	delayed	delayed	yes	no	*c.1682C>T (pPro5611Leu)*	missense
7	4	5	normal	delayed	delayed	yes	yes	*c.1031C>T (p.Pro344Leu)*	missense
8	5	11	delayed	delayed	delayed	no	no	*c.1031C>T (p.Pro344Leu)*	missense
9	4	18	normal	normal	normal	no	no	*c.949C>T, (p.Gln317*)*	stop gained

Table 1. *The psychomotor development of our patients at the last developmental follow up (dev.-development, dist.-disturbance) and the results of their molecular genetic testing*

Seizures were initially therapy resistant in nearly all patients, and the ineffectiveness of the ASM necessitated multiple changes in the treatment. Valproic acid was the most frequently used first-line treatment (5 cases). At the time of the study, 7/9 patients were seizure free on ASM, the average seizure free period was 21 months (range: 4 months–7 years). One girl had been seizure free for 10 months on topiramate monotherapy. Two patients on bitherapy

(levetiracetam+valproic acid or levetiracetam+carbamazepine) remained seizure free for at least one year. Six children were taking three ASMs, and four of them were seizure free.

3.4 Discussion

According to international data, the prevalence of PCDH19 epilepsy is 3-5/100.000 live births in females.[3,4] Based on our study, we estimated a lower prevalence; it was 1 in 100.000 live births in females.

We have found a higher rate (4/9; 44%) of epilepsy in the family history than Smith et al.[5] (3/38; 8%) and Chen et al.[6] (28/113; 25%).

The mean age of the children at the time of the first seizure was 15 months (range 5-22 months), consistent with the results (14 months) of Scheffer et al.[7] In more than half of the girls, the first seizure appeared focal (5/9), and it occurred in clusters in seven out of nine cases. Smith et al.[5] also noted a predominance of focal (58%) and cluster (92%) seizures.

In three children, the first EEG examination showed no abnormalities, while in six cases bilateral epileptiform discharges were described. Dell'Isola et al.[8] reported the absence of typical interictal EEG abnormalities in PCDH19-related epilepsy.

Lotte et al.[9] identified brain anomalies as focal cortical dysplasia, hippocampal sclerosis or arachnoid cysts in 9/ 48 (19%) cases. We assessed higher prevalence of brain anomalies in our patients, in two third of the children abnormalities were revealed.

Lotte et al.[9] reported valproic acid, clobazam and bromide as the most useful ASMs, whereas Higurashi et al.[10] observed that bromide, clobazam and phenytoin are the most effective medications. We found clobazam to be less appropriate, as only two out of eight girls on clobazam became seizure free. Currently, three patients are receiving valproic acid, two of whom are seizure free. In line with the data of Higurashi et al.[10] and Chen et al.[6] we assess that carbamazepine is not effective in treating PCDH19-related epilepsy.

In line with the observations of Lotte et al.[9], we found that eight of the nine girls showed mild/moderate intellectual development delay. Autism spectrum disorder was identified in two third of the children. Marini et al.[11] and Chen et al.[6] observed a lower rate (31.5%; 11/35 and 43%; 49/113) of autism spectrum disorder.

3.5 Conclusions

Compared to the published data, PCDH19-related epilepsy occurs less frequently (approximately 1/100.000 female live births) in the Hungarian population of children. In our study, almost half of our patients had a positive family history of epilepsy. In comparison to the previous studies, we found a higher proportion (7/9) of status epilepticus in our patients. We observed more frequent structural brain anomalies associated with epilepsy or incidental cerebral abnormalities on brain MRI. The most effective ASMs were valproic acid, clobazam and levetiracetam. More than two third of our patients were seizure free with combined ASM, but only one girl was receiving monotherapy.

Our study confirms that molecular genetic testing, including PCDH19 pathogenic variants, is recommended for female patients with an onset of seizure clusters before the age of three years.

4 Childhood and juvenile absence epilepsy

4.1 Introduction

Childhood and juvenile absence epilepsies (CAE and JAE) are classified as genetic generalised epilepsies according to the ILAE. Classification approved in 2022.[12] CAE starts typically between 4 and 10 years of age. It accounts for 10-17% of all childhood epilepsies diagnosed in children <15 years of age. The onset of JAE is between 7-16 years and included 2-3% of all epilepsies.[12-16] For many decades, childhood absence epilepsy was considered as a benign epilepsy syndrome. However, there is growing evidence that even with adequate seizure control, childhood epilepsy with absence seizures are often associated with impaired cognitive function and language skills.[17,18]

4.2 Patients and methods

In our retrospective study, data were collected from both electronic (e-MedSolution medical documentation system) and paper-based medical records of inpatients and outpatients who were diagnosed/followed up at the Division of Neurology, Department of Paediatrics, University of Pécs. In addition, data from the EEG database of the Electrophysiology Laboratory were used.

We collected and analysed data from patients diagnosed/treated with CAE or JAE between 2002 and 2021.

I assessed the followings in the children's medical records:

- perinatal history (birth weight, gestational age)
- family history of febrile seizures, epilepsy, or other neurological disorders
- own history of febrile seizures or other neurological disease
- age at the time of first absence seizure
- the time between the onset of absence seizures and the diagnosis of epilepsy syndrome
- the time between starting of ASM and seizure free status
- ASM, the effectiveness of the first, second and third choice ASM, occurrence of side effects
- relapse after ASM discontinuation, the time between ASM withdrawal and relapse
- development of other seizure type/s
- results of brain MRI

Children were classified as CAE or JAE according to their age, JAE was diagnosed after the onset of absence seizures >10 years.

The first, even ASM free EEG recording of all patients was precisely analysed.

All patients got ASM at least three years long after the diagnosis of CAE/JAE. Children were classified as cured if they had been seizure free at least two years after ASM discontinuation.

All statistical analyses were performed using the Excel 2013 and SPSS version 28.0 statistics software. Chi-square test was used to investigate the influences of different categorical variables on long-term outcome. We used Fisher's test to examine the relationship between the number of ASMs and prognosis.

4.3 Results

	CAE	JAE	CAE+JAE
Number of patients	60	16	76
Female	31	14	45
Family history of epilepsy	16	3	19
Family history of febrile seizure	1	-	1
History of febrile seizure	-	3	3
Only absence seizures	49	11	60
GTC seizure after absence seizures	11	5	16
Seizure free after first ASM	34	10	44
ASM discontinuation	45	14	59
Relapse	12	4	16
Seizure free without ASM	40	12	52

Table 2. *Clinical characteristics of CAE/JAE (GTC=generalized tonic-clonic)*

The average age at the onset of absence seizures was 7.9 years (range 1-15 years±3.3 SD). *(Table 2)*

We could analyse the first EEG recordings of 66 patients precisely. Hyperventilation (HV) was performed in 59 cases, absence seizure was provoked by HV in 49 (83%) children. The average number of seizures was five (range 1-21) during the recording. The average duration of the seizures was 8.1 seconds (range 1-40 seconds).

Brain MRI was performed in 29/76 of our patients and 10/29 (34 %) had abnormal findings. Left hippocampal malrotation was found in three children. In one case mild left hippocampal sclerosis, in one girl Arnold Chiari I malformation, in one patient focal cortical dysplasia was

observed. In another four cases incidentally identified benign alterations on brain MRI were found (slight left hippocampal abnormalities in two cases, left temporal white matter alterations, ventricular asymmetry+right thalamic vascular malformation).(

The first choice of ASM was valproic acid in 53/76 children (42%); 14 children got ethosuximide, and nine lamotrigine. *(Table 3)* Seizure freedom was achieved with first-line ASM in 59% (45/76) of the cases but six patients required a new medication due to side effects. Valproic acid had significant higher effectiveness than ethosuximide and lamotrigine (p=0.003).

	VPA	ETX	LTG
Number of patients Total: 76 patients	53	14	9
Seizure free	38 (72%)	4 (29%)	3 (33%)
ASM discontinuation	29	4	1
Relapse	7	1	0
Cured from epilepsy	21	3	1

Table 3. *First-line antiseizure medication and its effectiveness (VPA: valproic acid, ETX: ethosuximide, LTG: lamotrigine)*

37/76 (48.7%) children needed a second-line ASM, because of ineffectiveness of first ASM or occurrence of side effects. *(Table 4)*

	VPA	ETX	LTG	LEV	VPA+LTG	VPA+ETX
Number of patients (Total: 37)	11	8	6	1	8	3
Seizure free	7 (58%)	5 (62%)	5 (71%)	0	4 (50%)	0
ASM discontinuation	1	3	4	0	2	0
Relapse	0	1	2	0	0	0
Cured from epilepsy	1	1	2	0	2	0

Table 4. *Second-line antiseizure medication and its effectiveness (VPA: valproic acid, ETX: ethosuximide, LTG: lamotrigin,)*

Another monotherapy was ordered in 26 children, and 11 patients got combination therapy (add on ASM to the first choice ASM). New monotherapy had higher effectiveness (65%; 17/26), than the combination therapy (36%; 4/11). 19/76 (25%) children required a third-line ASM.

ASM was discontinued in 59/76 (78%) patients after three years seizure free status. 16/59 (27%) relapsed in 1-52 months (an average of 17 months). At the time of the study 52/76 (68%) of our patients were seizure free without ASM.

4.4 Discussion

We found a lower rate of epilepsy in the family history of our patients (19/76; 25%) than the previous studies (Bashiri[19] 17/35; 48.6%, Sadleir[20] 21/47; 45%, Amianto[21] 34%; 35/10). The data are variable regarding febrile convulsions in the history of children (8.5%-18.9%).[22,23] In our study, we observed a slightly lower value (3/76; 3.8%). The average age of the children at the time of the absence seizure onset was 7.9 years, consistent with the observations of Kim et al[17].

Based on the international guidelines, brain MRI is not required in the diagnostic work-up of CAE and/or JAE.[12] Amianto et al.[21] reported abnormalities on brain MRI in 16% (17/106) of children. 29/79 of our patients had brain MRI due to headache/ASM ineffectiveness, in 10/29 (34%) cases abnormal findings were revealed.

The average duration of the seizures was 8.1 seconds (range 1-40 seconds). Sadleir et al.[20] reported a similar duration (9.4 seconds; range 1-44 seconds). We observed >20 sec seizure in 5/66 (6.6%) cases, this result is lower than in other studies (Sadleir[20] 10/47, 21%; Dlugos[24] 129/440, 29%). Our observations regarding the median total seizure duration (1.85%) closely align with those of Dlugos et al.(1.5%).[24] In our study children with longer total absence seizure duration (more than 2%) on the first EEG were more likely to have a relapse after ASM discontinuation (p=0.021).

According to evidence based medicine ethosuximide, valproic acid or lamotrigine are proposed as first-line ASMs in CAE and/or JAE. [25] 45/76 (59%) of our patients were seizure free after starting ASM therapy. The most effective ASM was valproic acid; 38/53 (72%) children became seizure free. Other authors (Glauser[26] 85/146; 58%, Canafoglia[27] 91/117, 77.8%) found valproic acid also effective in absence epilepsy. There are controversial findings on the usefulness of ethosuximide. We described a lower response rate (29%; 4/14), than the previous studies (Glauser[26] 82/155; 53%, Hwang[28] 40/48; 84%). Our patient's response rate (33%) in the case of lamotrigine is consistent with the result of the study by Glauser et al.[26] (29%).

Nearly half of our patients (37/76; 48.7%) required second-line ASM. Another monotherapy was ordered in 26 children, and 11 patients got combination/add-on therapy. The most common second-line ASM was valproic acid (11 children), eight patients needed ethosuximide and six children got lamotrigine. In all cases, further seizure freedom was achieved: lamotrigine was successful in 71%, ethosuximide in 62 %, and valproate in 58%.

Lamotrigine+valproic acid bitherapy was effective in half of our patients. Three children required ethosuximide+valproic acid combination but none of them became seizure free. Second-line monotherapy was effective in 65% (17/26) of our patients and 36% (4/11) of children with combination therapy were seizure-free.

Male gender, history of febrile seizure, epilepsy in the family history, absence status epilepticus, myoclonic and/or generalized tonic-clonic seizures, pharmacoresistance are unfavourable prognostic factors.[21,29,30] We have not observed significant association between the prognosis and gender, positive family history, age at the time of the first absence seizure.

In line with Amianto et al.[21], we observed that children who needed at least three different ASMs have a higher risk of relapse after ASM discontinuation (p=0.008). The relapse rate (27%) was higher than in the study by Canafoglia et al.[27] (14,2%), Amianto et al.[21] (17%).

4.5 Conclusion

Based on our research findings, CAE and JAE not always can be considered benign epilepsy syndromes, because:

- the first choice of ASM was effective only in 45/76 (59%) cases
- nearly half of the children (37/76; 48.7%) required second-line ASM therapy due to ineffectiveness/side effects of ASMs
- 19/76 (25%) children needed third-line of ASM
- 16/59 (27%) patients had seizure relapse after ASM discontinuation

Valproic acid had significant higher effectiveness than ethosuximide and lamotrigine. When the first choice of ASM was not useful, a second-line monotherapy was more effective than an add-on combination therapy (65% vs. 36%).

According to our data, relapse occured more frequently when

- patients had longer duration of total absence seizure on the first EEG examination
- at least three different ASMs were used during treatment period.

5 SARS-CoV-2 infection and febrile convulsion

5.1 Introduction

The incidence of febrile convulsions in Europe is 2-5%, it occurs typically between the ages of 0.5-5 years. Febrile convulsions happen most often in connection with influenza, adeno-, parainfluenza, and herpes virus infections, but they can also occur due to bacterial infections or after vaccinations.[31] SARS-CoV-2 infection develops less frequently in childhood than in the adult population. With the spread of the Omicron variant, the number of infections, hospitalizations and neurological manifestations in the age group younger than 18 years gradually increased.[32]

5.2 Patients and methods

We collected the clinical data of children aged 0-6 years who were at our university hospital due to febrile convulsions from 1 February 2020 to 1 February 2022. The data were reviewed from the electronic database based on the diagnosis of febrile convulsion (ICD International Classification of Diseases code R5600). We examined the following data: perinatal history, familial history, age of the patients at the time of febrile convulsion, the type of febrile convulsion (simple or complicated), own history of neurological disease. Simple febrile seizure was defined as a seizure which occurs with high fever, affects both sides of the body, lasts for a short time, happens only once during a febrile illness, and is not associated with residual neurological symptoms. SARS-CoV-2 infection was confirmed with the Panbio-Abbott or GENEDIA W (Green Cross Medical Science Corp.) Covid-19 rapid antigen tests and/or RT-PCR method.

Patients who were treated due to febrile convulsions at the same university hospital from 1 January 2018 to 1 January 2020 generated the control group.

All statistical analyses were performed using the Excel 2013 and SPSS version 26.0 statistics software.

5.3 Results

From 1 February 2020 to 1 February 2022, a total of 11318 children were admitted to our university hospital. 113 children under the age of six had laboratory-confirmed SARS-CoV-2 infection. In this period 51 patients were treated with febrile convulsions, but only four of them (7.8 %) had laboratory confirmed SARS-CoV-2 infection. In three cases, the results of both the rapid Covid-19 antigen test and the PCR test were positive, in one child, only the

rapid Covid-19 antigen test was positive. Three patients were affected during the Omicron variant period. Three patients had their first febrile convulsion, one child had a history of two previous febrile seizures. Simple febrile convulsion was registered in three cases, only one child had complicated febrile seizure.

During the control period a total of 15375 children were examined in our university hospital, among them 66 had febrile convulsion.

In both the control and pandemic periods 0.4 % of the children were hospitalized because of febrile convulsions (66/15375 children and 51/11318 children).

	Febr 2018-Febr 2020 Number of patients (%) Total: 66 persons	**Febr 2020 – Febr 2022 Number of patients (%) Total: 51 persons**	**p-value**
Gestational age	40 (38-40) weeks	39 (38-40) weeks	0.362
Age of the children at the time of febrile convulsion	2.25 (1.5-3.2) years	1.9 (1.0-2.85) years	0.125
First febrile seizure	52 (78.8%)	44 (86.3%)	0.902
Simple febrile seizure	59 (89.4%)	40 (78.4%)	0.062
Complicated febrile seizure	7 (10.6%)	11 (21.6%)	0.298
Febrile seizure in the family history	12 (18.2%)	6 (11.8%)	0.362
Epilepsy in the family history	10 (15.2%)	6 (11.8%)	0.481

Table 5. *Occurrence and characteristics of febrile seizures before and during the coronavirus pandemic*

No statistically significant difference was found between the data of the two periods. *(Table 5)*

5.4 Discussion

During the different waves of the coronavirus pandemic, a variety of information has been available regarding the occurrence of febrile convulsions.[33] In our study, only four (3.5%) of 113 confirmed SARS-CoV-2 infected children under the age of six had febrile convulsion during the pandemic period. Smarrazzo et al.[34] observed 56 children due to febrile convulsions, of which two (3.5%) had confirmed coronavirus infection. During the pandemic, we found SARS-CoV-2 infection in only four (7.8%) of the 51 children who produced febrile convulsion. Similar to the data of Hanlon et al.[35], our patients predominantly had simple febrile convulsions

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We found no statistically significant difference in the age of children with febrile convulsions in the period before and after the coronavirus pandemic (2.4 and 2.2 years) either. In both time periods, most children (78.8 % and 86.3 %) had their first febrile convulsion.

Our data harmonize with the internationally reported findings that the prevalence of febrile convulsions increased during the period of the Omicron variant. In our study, three out of four children had febrile convulsions during the Omicron variant. Iijima et al.[33] found febrile convulsions in 14.6 % (22/151) of febrile children during the Omicron variant, and only 1.7 % (2/115) of patients in the preceding period.

5.5 Conclusions

We can conclude that during the pandemic caused by the SARS-CoV-2 infection, we did not experience more frequently febrile convulsions, than in the period before the pandemic. We also found no difference in the age of the children at the onset of the first febrile convulsion. Looking at the different periods of the coronavirus pandemic, it seems that more febrile convulsions occurred during the Omicron variant than in the previous periods. Our observation harmonizes with the international data.

6 Responses to objectives, summary of the novel results

6.1 PCDH19 epilepsy

The aim of our retrospective, multicentre study was to establish database of 0-18 years old patients with genetically confirmed PCDH19 epilepsy , to determine the Hungarian prevalence of this rare epileptic encephalopathy, to collect the clinical, imaging and EEG characteristics and to define the optimal ASM treatment.

Compared to the international data (3-5/100.000 female live births), we found a lower prevalence of PCDH19-related epilepsy (approximately 1/100.000 female live births) in the Hungarian population under 18 years.

Comparing to previous findings, we got a higher rate (4/9) of epilepsy in the family histories of our PCDH19 patients.

The first seizure arrived in cluster in 7/9 cases. Status epilepticus was more frequent in our patients (7/9) compared to the reported data. We found higher prevalence (6/9) of structural/benign brain anomalies in our patients as reported previously.

We observed autistic symptoms in two third of our patients. Only one child had normal intellectual development.

The most effective ASM were valproate, clobazam and levetiracetam. 7/9 of our patients have been seizure-free on ASM, but only one child was receiving monotherapy.

It can be anticipated that the widespread use of molecular genetic testing will lead to an increase of the incidence of PCDH19 gene pathogenic variant-related diseases. Molecular genetic testing for PCDH19 pathogenic variants is strongly recommended for girls whose seizures begin before the age of three years and occur in clusters.

The Network for Therapy of Rare Epilepsies (NETRE) collects data about patients with PCDH19 epilepsy. In NETRE I am currently one of the coordinators for PCDH19 epilepsy. Further goals include assessing the prevalence of PCDH19 epilepsy in the adult population and collecting clinical data.

6.2 Childhood and juvenile absence epilepsy (CAE and JAE)

The aim of our study was to examine the clinical data, EEG and brain MR results, prognosis of children with CAE and JAE. A key question was whether childhood and juvenile absence epilepsies are really as benign as previously believed—before the widespread availability of more precise diagnostic methods.

Our investigation has led to the following conclusions:

Comparing to the studies published we found lower prevalence (25%; 19/76) of positive family history of epilepsy in our patients with CAE and JAE.

Although brain MRI is not part of routine diagnostic work-up for childhood absence epilepsy, MRIs are often performed for research purposes. We valued brain anomalies in 34% of our studied children on brain MRI.

According to the Cochrane database, the suggested first-line treatment are ethosuximide, valproic acid or lamotrigine in patients with absence epilepsies. In our study, valproic acid led to a statistically significantly higher rate of seizure freedom compared to ethosuximide or lamotrigine. The first choice ASM was effective in 45/76 (59%) cases.

We found no clear recommendations in the international scientific literature regarding whether, in the case of first choice ASM failure, switching to another monotherapy or combining the initial ASM with another drug would be more effective. According to our results, introducing a new ASM is more successful than adding a second drug to the original monotherapy (65% vs. 36%).

Compared to published data, we found a higher rate (16/59; 27%) of relapse after ASM discontinuation. We investigated whether clinical and EEG characteristics might influence the prevalence of relapse. We found that relapse after ASM discontinuation was more common when absence seizures (3 Hz spike-wave paroxysms) occurred in a higher percentage during the first EEG examination, and when at least three different ASMs were required during the treatment period.

6.3 SARS-CoV-2 infection and febrile convulsion

Focusing on febrile convulsions among the neurological manifestations observed during the COVID pandemic, we studied whether the frequency of febrile convulsions changed during the COVID-19 pandemic compared to the pre-pandemic period?

Based on our data, SARS-CoV-2 infection does not increase the risk of febrile convulsions. No difference was found between the pandemic and pre-pandemic control periods considering the age of the children at the onset of febrile convulsion or the types of the febrile convulsions.

However, analysing the different phases of the coronavirus pandemic, we noticed that febrile convulsions occurred more frequently during the Omicron variant period. This observation is consistent with findings of the published international data.

7 References

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8 Publications related to this thesis

8.1 Publications

1. **Kovacs M**, Fogarasi A, Hegyi M, Siegler Zs, Kelemen A, Monika M, Orbok A, Simon G, Farkas K, Bessenyei M, Hollody K (2024) Multicenter retrospective study of patients with PCDH19-related epilepsy: The first Hungarian cohort. Epileptic Disord. 2024 Jul 17 **[IP: 1.9]**
2. **Kovacs M**, Makszin L, Nyul Z, Hollody K (2024) Has the Incidence of Febrile Convulsions in Childhood Changed During the SARS-CoV-2 Pandemic? J Child Neurol. 2024;39(5-6):190-194. **[IP: 2.0]**

8.2 Presentations

1. **Kovács Mónika**, Hollódy Katalin, Nagy Eszter. Gyermekkori absence epilepszia. Valóban olyan jó a prognózis? *PTE ÁOK Tudományos Diákköri Konferencia, Pécs, 2019. Közönségdíj*
2. **Kovács Mónika**, Hollódy Katalin, Nagy Eszter. Gyermekkori absence epilepsziák kórjóslata. *Korányi Frigyes Tudományos Fórum, Budapest, 2019*
3. **Kovács Mónika**, Hollódy Katalin, Nagy Eszter. Gyermekkori absence epilepsziák. Valóban olyan jó a prognózis? *Magyar Gyermekgyógyász Társaság Kongresszusa, Eger, 2019*
4. **Kovács Mónika**, Hollódy Katalin, Péter István. Miller-Fisher szindróma. Magyar Gyermekneurológiai Társaság Kongresszusa, Budapest, 2021
5. **Kovács Mónika**, Péter István, Simon Gábor, Hegyi Márta, Fogarasi András, Till Ágnes, Hadzsiev Kinga, Hollódy Katalin. Epilepszia, autizmus spektrumzavar tünetei PCDH19 mutáció következtében. *Magyar Gyermekneurológiai Társaság Kongresszusa, Balatonfüred, 2022*
6. **Kovács Mónika**, Bessenyei Mónika, Farkas Márk Kristóf, Fogarasi András, Hegyi Márta, Kelemen Anna, Mellár Mónika, Orbók Anna, Siegler Zsuzsanna, Simon Gábor, Hollódy Katalin. PCDH19 epilepszia, tünetek és lefolyás a magyar betegpopulációban. *Magyar Gyermekneurológiai Társaság Kongresszusa, Debrecen, 2023*

7. **Kovács Mónika**, Péter István, Makszin Lilla, Hollódy Katalin. Az egy éves életkor előtt kezdődő epilepsziák klinikuma és prognózisa. *Magyar Gyermekneurológiai Társaság Kongresszusa, Székesfehérvár, 2024*
8. **Kovács Mónika**, Péter István, Makszin Lilla, Hollódy Katalin. A gyermekkori absence epilepszia klinikuma és prognózisa. *Magyar Gyermekneurológiai Társaság Kongresszusa, Kecskemét, 2025*

8.3 Posters

1. **Kovács Mónika**, Nyul Zoltán, Hollódy Katalin. Lázas görcs előfordulása a Covid-19 pandémia ideje alatt. *Magyar Gyermekorvosok Társasága Kongresszusa, Kecskemét, 2022*
2. **Kovács Mónika**, Bessenyei Mónika, Farkas Márk Kristóf, Fogarasi András, Hegyi Márta, Kelemen Anna, Mellár Mónika, Orbók Anna, Siegler Zsuzsanna, Simon Gábor, Hollódy Katalin. Clinical description of 9 patients with PCDH19 mutation. A multicentre retrospective study. *European Peadiatric Neurology Society (EPNS) Congress, Prága, 2023*
3. **Kovács Mónika**, Bessenyei Mónika, Farkas Márk Kristóf, Fogarasi András, Hegyi Márta, Kelemen Anna, Mellár Mónika, Orbók Anna, Siegler Zsuzsanna, Simon Gábor, Hollódy Katalin. Egy ritka genetikai epilepszia szindróma. *Magyar Gyermekorvosok Társasága Kongresszusa, Keszthely, 2023*
4. **Kovács Mónika**, Péter István, Makszin Lilla, Hollódy Katalin. Long-term outcome of childhood absence epilepsy. *European Peadiatric Neurology Society (EPNS) Congress, München, 2025*

9 Acknowledgments

First of all, I would like to thank my supervisor and mentor, Professor Katalin Hollódy, who has helped my work since I was a medical student. Without her encouragement, continuous support, excellent ideas and indispensable advice this thesis could not have been written.

I express my gratitude to Professor Tamás Decsi for providing the opportunity for my research at the Department of Paediatrics, University of Pécs.

I would like to thank Professor József Janszky for his support throughout my PhD work.

I am very grateful to Lilla Makszin who helped me with the statistical analysis.

Gábor Rébék-Nagy willingly supported me with the English translation.

I am grateful to all colleagues of the Division of Paediatric Neurology and to the assistants of the EEG-lab for the support of my research work.

I appreciate the kind helpfulness of the peaediatric neurologists Professor András Fogarasi, Marta Hegyi, Zsuzsanna Siegler, Anna Kelemen, Mónika Mellár, Anna Orbók, Gábor Simon, Kristóf Farkas, Mónika Bessenyei for answering the questionnaire for children with PCDH19 epilepsy.

Dr. Zoltán Nyul helped my research work with his instructions.

Last, but not least, my special thanks go to my family and my friends for their patience, understanding, continuous encouragement.