Paediatric Neurological Disorders: From Benign Paroxysmal Events to Severe Cerebral Palsy

Doctoral (PhD) Thesis

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I. Introduction

Paediatric neurology is one of the most far-reaching and interesting fields of medicine. It deals with newborns, infants, children, and adolescents requiring acute, intensive or chronic care, and this is what makes it challenging. Paediatricians, paediatric neurologists usually ask the age of their patients first, because certain diseases only occur at a specific age. For example, West syndrome does not manifest in the adolescent age, while juvenile myoclonic epilepsy does not begin in infancy. Nevertheless, self-limited benign disorders appear only at a specific age, but similar signs or symptoms could refer to severe neurological diseases.

During my research, I have focused on three seemingly separate, but strongly connected parts of paediatric neurology.

II. Differential diagnosis of neonatal and infantile paroxysmal events

II.1. Literature review

The identification and differentiation of seizures without electroencephalography (EEG) belong to the most complicated tasks for paediatric neurologists. This occurs especially during the neonatal period and in the early infancy, where the differential diagnosis of the pathological and physiological movements require much effort. Subtle seizures (motor automatisms of the tongue and/or face; horizontal deviation of the eyes with or without nystagmus; fixation of the eyes; munching, boxing, pedalling or cycling movements) of the young infants (especially in premature babies) are challenging to recognize.

Malone et al.[1] got surprising results studying the paroxysmal events of newborn babies: in only 54% of the cases neonatologists were able to correctly judge the epileptic or nonepileptic origin of different movement types (based only on videorecordings), while nurses were successful in 48%.

Based on these results, we can conclude that the recognition of neonatal and infantile paroxysmal events without EEG is extremely inaccurate. For that reason, an infant with epilepsy may remain without antiepileptic treatment, while another infant with benign movements may get unnecessarily anticonvulsive drugs.

II.2. Aims

A) Firstly, we aimed to record neonatal and infantile paroxysmal events on videos in order to compare the movements with the child's history and the description of the movement given by parents. Additionally, we intended to provide a useful tool with description of movement characteristics and video examples for those physicians facing with such cases for the first time (general practitioners, emergency physicians or paediatric neurologists).

B) Secondly, we also wanted to measure the proportion of correct seizure recognition which we achieved by presenting the videos to groups of individuals with different medical qualifications (first- and 4-5th-year medical students, paediatric residents, paediatric neurologists, adult neurologists and parents). We hypothesised positive correlation between higher education and more correct recognition of paroxysmal events.

C) Thirdly, we wanted to estimate the difference between the assessments of the neonatologists, paediatric neurologists, and neurologists as well considering the common paroxysmal events of infancy. We hypothesised that disagreement would be found between the groups of specialists not only in the correct treatment of the neonatal seizures,[2-4] but in the assessment of the different paroxysmal events.

II.3. Paroxysmal nonepileptic events in neonates and infants

Photo and video documentations were created about the paroxysmal, nonepileptic events in neonatal age and infancy. Characteristic history and the description provided by parents were also assigned to the photo and video documentations. Documented events included benign neonatal/infantile sleep myoclonus, jitteriness, shuddering attack, paroxysmal tonic upgaze and infantile gratification (masturbation).

Nagy E, Hollódy K. Paroxysmal nonepileptic events in infancy: five cases with typical features. Epileptic Disorders. [accepted for publication]

II.4. Differential diagnosis of epileptic and nonepileptic paroxysmal events occurring in neonates and infants

II.4.1. Patients and Methods

From the video-EEG database of the Department of Paediatrics, University of Pécs 15 videos *(Table 1)* were chosen according to some criteria. The average duration of the videos was 30 seconds. Only video recordings (without EEG recording and any additional history data) were displayed for the six groups.

Groups and their features:

- 159 first-year medical students,
- 65 fourth or fifth-year medical students,
- 52 paediatric residents and
- 18 paediatric neurologists from different European countries (who participated in the EPNS Training Course, Budapest 2016)
- 43 neurologists attended the Education and Training Course of Neurophysiology in Debrecen 2017
- 37 parents. The children of these parents have been followed up regularly at the Outpatient Service of Child Neurology at Department of Paediatrics.

Each video was presented only once. Nine children were diagnosed with epileptic seizure, six children showed other benign movements. The participants were given a paper-based questionnaire, and they were requested to answer immediately after watching each video. They had to decide whether or not the movement of the child was an epileptic or non-epileptic event. In advance, they were informed about the purpose of the study and ensured the anonymity of their answers.

The data were collected by Microsoft Office Excel 2013. Correct answer rate (CAR) was calculated in each group and for every video. The statistical analyses were performed by IBM SPSS Statistics 24. The level of significance was set at 0.05.

Number of the video	Age and gender of the child	Visible movements on the video recording	Aetiology-Diagnosis	Epilepsy or not?
1.	2 days, male	continuous tremor of four limbs	hypoxic-ischaemic encephalopathy	yes
2.	2 months, male	rhythmic, tremor like movements involving four limbs	jitteriness	no
3.	4 months, female	clonus of the right arm	left temporooccipital cortical dysplasia	yes
4.	7 days, female	horizontal nystagmus to the right side	congenital hydrocephalus	yes
5.	14 days, male	the examiner knocks the nose of the baby, he becomes stiff for a moment and produces a myoclonus-like movement	hyperekplexia	no
6.	5 months, male	continuous horizontal shaking of the head with munching	Alexander leukodystrophy	yes
7.	5 months, female	very discrete finger rubbing movements on the left hand	Septo-optic dysplasia	yes
8.	7 days, male	asymmetric myoclonic jerks involving four limbs	non-ketotic hyperglycaemia	yes
9.	2 months, male	subtle myoclonic jerks of four limbs during sleep	benign neonatal sleep myoclonus	no
10.	5 days, male	tremor of the lower limbs	jitteriness	no
11.	2 months, female	rhythmic, tremor like movements involving four limbs which can be stopped by touching of the limbs	jitteriness	no
12.	10 days, male	high amplitude, rough tremor of four limbs	infant of a drug addict mother (heroin)	no
13.	2 months, male	rough myoclonia dominantly of arms	non-ketotic hyperglycaemia	yes
14.	2 days, male	sudden, synchronised extension of the arms	polymicrogyria	yes
15.	5 months, male	in supine position repeating elevation of the arms and lower extremities with the flexion of neck	epileptic spasms, West syndrome	yes

Table 1 Characteristics of patients and videos

II.4.2. Results (*Table 2*)

5610 answers were evaluated, 2766 of them (49.3%) were correct. The average experience of paediatric neurologists was 5.3 year (range between 0-16 years) after their license exam. The lowest average CAR was given by the first-year medical students (36.6%). The highest average CAR was reached by the paediatric neurologists (67.4%).

We performed one-way ANOVA, which showed the presence of a significant difference in the CAR by videos at least between two groups (p=0.007). Further Post-Hoc (Bonferroni) tests were used to reveal which groups differ from each other. A significant difference was found between the answers of 1st-year medical students and residents (p=0.045), furthermore between the responses of 1st-year medical students and paediatric neurologists (p=0.02).

	1st-year-students		4-5th-year-students		residents		paed. neur.		neurologists		parents		all correct answer	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
1	142	89.3%	60	92.3%	21	40.4%	9	50.0%	20	46.5%	31	83.8%	283	75.7%
2	87	54.7%	37	56.9%	28	53.8%	14	77.8%	18	41.9%	20	54.1%	204	54.5%
3	17	10.7%	53	81.5%	24	46.2%	6	33.3%	20	46.5%	7	18.9%	127	34.0%
4	107	67.3%	33	50.8%	50	96.2%	18	100%	36	83.7%	29	78.4%	273	73.0%
5	137	86.2%	49	75.4%	48	92.3%	17	94.4%	37	86.1%	30	81.1%	318	85.0%
6	13	8.2%	52	80.0%	37	71.2%	13	72.2%	14	32.6%	12	32.4%	141	37.7%
7	1	0.6%	40	61.5%	12	23.1%	4	22.2%	6	14.0%	5	13.5%	68	18.2%
8	131	82.4%	27	41.5%	44	84.6%	18	100%	37	86.1%	28	75.7%	285	76.2%
9	122	76.7%	28	43.1%	39	75.0%	13	72.2%	20	46.5%	24	64.9%	246	65.8%
10	20	12.6%	26	40.0%	29	55.8%	7	38.9%	27	62.8%	13	35.1%	122	32.6%
11	10	6.3%	22	33.8%	43	82.7%	14	77.8%	35	81.4%	10	27.0%	134	35.8%
12	4	2.5%	20	30.8%	37	71.2%	11	61.1%	25	58.1%	1	2.7%	98	26.2%
13	29	18.2%	42	64.6%	34	65.4%	9	50.0%	28	65.1%	17	45.9%	159	42.5%
14	26	16.4%	63	96.9%	29	55.8%	14	77.8%	35	81.4%	7	18.9%	174	46.5%
15	27	17.0%	20	30.8%	32	61.5%	15	83.3%	27	62.8%	13	35.1%	134	35.8%
all	873	36.6%	572	58.7%	507	65.0%	182	67.4%	385	59.7%	247	44.5%	2766	49.3%

Table 2 *Number and percentage of the correct answers (CAR) in six groups (paed. neur. abbreviation for paediatric neurologist)*

Video 7 proved to be the most difficult to differentiate for the participants. The very discrete finger rubbing movements of a 4-month-old baby with septo-optic dysplasia were deceptive. The average CAR was only 18.2%. The majority of the responders (average CAR 85%) recognised the baby with hyperekplexia (No. 5.) correctly.

Surprisingly, the videos 4 and 8 seemed to be very clear to the paediatric neurologists, 100% of them gave a correct answer. On video 4 a baby with nystagmus, on video 8 a young infant with violent, asymmetric, repeated myoclonus were seen. Nystagmus as a cranial nerve sign and a very violent myoclonus call attention to severe neurological diseases.

II.4.3. Discussion

The appearance of neonatal and infantile seizures can mislead not only medical students and parents but experienced paediatric neurologists also. Malone et al.[1] studied neonatal seizure identification among health care professionals (91 medical doctors, 46 nurses). We wanted to extend our measures not only to staff specialised in neonatal care, but we were curious about the results for students and doctors at different levels of medical education. Infants with unusual movements are examined first by family doctors, not specialists, and they will refer them to clinics if it is necessary. We modulated the age criteria of babies, as well. We displayed video recordings not only about neonates but also older infants (2 days-5 months). Another difference between Malone's[1] and our findings is, that we extended our survey to parents as well because they are usually the first witnesses of the seizures. We think it is extremely important that weird, extra movements of children draw the attention of parents and they visit their family doctor as soon as possible.

Our research data supported our hypothesis. Those groups of participants with higher qualifications were found to evaluate the epileptic or nonepileptic origin of the presented movements more correctly. As we expected, the best result was reached by the paediatric neurologists (67.4%), while the lowest average correct answer rate was given by the first-year medical students (36.6%). Significant difference was found between the answers of 1st-year medical students and residents ($p=0.045$), and between the responses of 1st-year medical students and paediatric neurologists ($p=0.02$).

Another difference between Malone's and our findings is that we extended our survey to parents as well because they are usually the first witnesses of the seizures. We think it is extremely important that weird, extra movements of children draw the attention of parents and they visit their family doctor as soon as possible. The results of parents seemed to be better, than first-year medical students, which can be explained by the fact, that they have at least one child, who suffers from some kind of neurological disease, mostly epilepsy.

In Malone's study[1] the neonatologists assessed 11.9/20 video clips correctly (59.5%). This value is similar to the result of the international paediatric neurologist group in our survey (67.4%). In Malone's study, participants knew the past medical history, but in our study, the responders were not informed about the previous history of the infants. Based on these results, we suppose that the level of paediatric neurology training is comparably adequate. However, this conclusion is limited, because videos presented in the studies are not identical.

Nagy E, Major A, Farkas N, Hollódy K. Epileptic seizure or not? Proportion of correct judgement based only on a video recording of a paroxysmal event. Seizure 2017; 53:26–30.

II.5. The evaluation of paroxysmal events in neonates and infants. Do neonatologists, paediatric neurologists and neurologists differ in their opinion?

II.5.1. Methods

In this study, we aimed to reveal whether there is any difference in the opinion of neonatologists, paediatric neurologists and neurologists considering the assessment of common paroxysmal events in infancy.

The participants:

1) 47 paediatric neurologists that attended the conference of the Hungarian Paediatric Neurology Society in Pécs, Hungary 2017,
2) 25 neonatologists and 10 nurses working in Hungarian Neonatal or Perinatal Intensive Care Units participating in the conference of the Hungarian Perinatal Society in Tapolca, Hungary 2017,
3) the above-mentioned 43 neurologists that attended the Education and Training Course of Neurophysiology in Debrecen 2017.

II.5.2. Results

A total of 1230 responses were evaluated, of which 824 (67%) were correct. The average correct answer rate (CAR) of paediatric neurologists was 66%, while neonatologists judged correctly 69% of the cases.

96% (79/82) of the participants suspected epileptic seizure in a child with congenital hydrocephalus and nystagmus (Video 4). Video 7 and video 14 proved to be the most troublesome to differentiate for the participants. In both cases, 35.37% of the respondents were able to evaluate the very discrete finger rubbing movements of a 4-month-old infant with septo-optic dysplasia and the sudden, synchronized arm extension of a two-day-old infant correctly.

CARs were calculated separately for every video in the neonatologist (26–97%) and the paediatric neurologist group (21–96%). Comparing the 15-15 values by independent-samples t-test, no significant difference was found between their results ($p=0.72$).

To complete our study, we compared the answers of the paediatric neurologists with the results of the adult neurologists. No significant difference ($p=0.424$) was revealed in their CARs for the 15-15 videos. Based on the average CARs we can conclude, that paediatric neurologists were slightly more accurate (65.82% vs. 59.69%).

II.5.3. Discussion

In this study, we inquired and compared the opinion of neonatologists and paediatric neurologists about different neonatal and infantile paroxysmal events. No significant difference was found between their assessments as their evaluations were very similar (69 and 66%).

Hungarian data seems to be better compared to the results of Malone et al.[1] (54% vs. 69 and 66%). However, we would like to underline that different videos were presented in both studies. The result of our Hungarian paediatric neurologist group (66%) is almost

the same as the result of the international paediatric neurologist group from our previous research (67.4%). This may refer to the fact that the Hungarian paediatric neurology training meets the international standards.

The comparison of the results of paediatric and adult neurologists is really important because sometimes adult neurologists treat young patients (children). No significant difference was revealed between the answers of the two groups (66% vs. 59.7%).

Nagy E, Farkas N, Hollódy K. Paroxysmalis jelenségek megítélése az újszülött- és csecsemőkorban. Ideggyógyászati Szemle 2018; 71(9–10):313–319.

III. Aetiology and prognosis of patients with West syndrome. The occurrence of cerebral palsy in patients with West syndrome

III.1. Literature review

West syndrome (WS) is a rare epilepsy syndrome (its incidence ranges between 2-5/10000 live births), occurring in infancy (peak between 5 and 10 months). It is featured by a triad: infantile (epileptic) spasms, hypsarrhythmia on the EEG and neurodevelopmental regression.

Several pre-, peri- and postnatal factors can play a role in the development of WS. Its prognosis is especially poor, including epileptic and psychomotor outcome as well. Even if the cessation of spasms is successful, 50-60% of children will have other epileptic seizures again till the age of 5 years, while in 75-90% of them intellectual regression will occur.[5; 6] One part of children with WS is severely disabled and cerebral palsy (CP) is a common co-morbidity. The data are controversial on the co-occurrence of WS and CP in children and on the clinical features of this subgroup of CP as well.[5; 7-13] Wong et al.[12] found that 21% of children with WS had CP, while Watanabe et al.[9] reported that 95% of a selected population with WS had CP.

Several papers[14-19] have already been published about the MRI results and outcome of WS, but none of them compared the findings of the patients with WS regarding their CP status.

III.2. Aims

1/ to collect the patients (and their history) diagnosed and treated with West syndrome at the Department of Paediatrics, Clinical Center, University of Pécs,

2/ to measure the occurrence of CP in this special population by the examination of the patients and the analysis of the collected data,

3/ to assess and classify the possible causative factors of WS and CP with neuroimaging (MRI),

4/ to investigate and compare the main clinical features (cognitive function, walking ability and epileptic status of the patients) in the CP and non-CP groups.

III.3. Method

The children treated with WS between 01/01/1987-31/12/2016 in the Department of Paediatrics were enrolled in our retrospective, observational study.

The collected data

1. Perinatal data: sex, birthweight, gestational age, method of birth, age and corrected age at the first infantile spasm,
2. CP (and subtypes): patients were classified into CP and non-CP groups to compare the different clinical factors
3. Neuroimaging results
   All records were thoroughly and systematically reviewed for white matter, corpus callosum, hippocampus, thalamus, basal ganglia anomalies. Based on the clinical data and MRI results, patients were classified into seven groups considering the most remarkable disorder including hypoxia/ischemia, cerebrovascular insult, brain malformation, infection, inborn errors of metabolism, other anomalies and negative groups.
4. Walking ability: all patients were classified simply to either walking or non-walking groups.
5. Epileptic status: later, after the cessation of infantile spasms, epileptic status of the children were not precisely examined, only three groups were identified: 1/ seizure-free without medication for at least two years, 2/ seizure-free with ongoing medication, 3/ not seizure-free with ongoing medication.
6. Cognitive status: four groups were established: 1/ intact cognitive function (IQ≥70), 2/ mild (IQ 51-69), 3/ moderate (IQ 50-21), or 4/ severe intellectual disability (IQ≤20).

Differences between the two groups were statistically examined by IBM SPSS Statistics 24 (Armonk, NY: IBM Corp.) and RStudio (R.RStudio, Inc., Boston, MA). The level of significance was defined as 0.05.

III.4. Results

62 of the 74 patients with WS enrolled in the study were finally included, as 12 patients with missing MRI results have been excluded. 39/62 patients were affected by CP (CP group N=39, non-CP group N=23). 31/39 patients (80 %) had spastic tetraparesis and 6/39 (15 %) had spastic hemiparesis. One child had dystonic-dyskinetic type of CP, one had hypotonic CP.

III.4.1. Neuroimaging findings (MRI)

Main anomalies were brain malformation (21; 34%), hypoxic-ischemic encephalopathy (13; 21%), cerebrovascular insult (8; 13%), infection (7; 11%), cerebral atrophy (4; 7%) and inborn errors of metabolism (2; 3 %). In seven cases (11 %), no causative factor was revealed, and MRI results were negative as well. No structural abnormality of the brain or metabolic anomaly were found in one patient with CP *(Table 3)*.

Group (N)	CP group (39)	non-CP group (23)
Pre/perinatal hypoxia-ischemia	12	1
Cerebrovascular insult	7	1
-pre- and perinatal infarction	(3)	-
-intraventricular hemorrhage	(4)	(1)
Brain malformations	10	11
-lissencephaly	(3)	-
-colpocephaly	(1)	(1)
-cortical dysplasia	(2)	(1)
-polymicrogyria	(1)	(1)
-Aicardi syndrome	(1)	-
-subependymal heterotopia	-	(1)
-tuberous sclerosis	-	(3)
-others	(2)	(4)
Infection	7	-
-intrauterine toxoplasmosis	(2)	-
-intrauterine CMV infection	(1)	-
-acquired CNS infection	(4)	-
Inborn errors/ white matter lesions	-	2
-Leigh syndrome	-	(1)
-leukodystrophy	-	(1)
Other (cerebral atrophy)	2	2
Negative	1	6

Table 3 *MRI results/causative factors of the CP group and the non-CP group (N, number of participants; MRI, magnetic resonance imaging; CP, cerebral palsy; CMV, cytomegalovirus; CNS, Central Nervous System)*

In the CP group pre/perinatal hypoxia/ischemia(12/39; 31%) and brain malformations (10/39; 26%) were the most common causative factors, while in the non-CP group brain malformation(11/23; 48%) was found as the dominant cause of epilepsy, and the rate of pre/perinatal hypoxia/ischemia is very low (1/23; 4%).

Normal MRI and hippocampal anomalies were significantly more common in the non-CP group, while pathological white matter findings (excluding corpus callosum disorders) occurred significantly more frequently in the CP group.

III.4.2. Walking ability, epileptic and cognitive status

Significant difference was found in the distribution of walking ability, epileptic status and cognitive function in the CP and the non-CP groups.

In the non-CP group, 90% of the patients were able to walk. Those two patients who were unable to walk suffered from PEHO syndrome and leukodystrophy. In the CP group, 78% of patients had very severe gross motor retardation.

The rate of therapy-resistant epilepsy was higher in the non-CP group than in the CP group (67% vs. 54%). In the CP group among children who were on antiepileptic

medication, seizure-free status was more common than in the non-CP group. The rate of seizure-free patients without medication was similar in both groups (CP: 14%; nCP:19%).

Severe intellectual disability was approximately four times more frequent in the CP group (84% vs. 19%). Mild and moderate disability was more frequent in the non-CP group. No patient from the CP group had normal cognitive function.

III.5. Discussion

More studies[14-19] have already investigated the cranial MRI results and the prognosis of children with West syndrome, to our knowledge, this is the first study which investigates separately the neuroimaging findings, walking ability, cognitive function and epileptic status of patients with WS according to their motor status.

III.5.1. MRI results

In 88.7 % of our patients with WS, pathological anomaly was found on MRI. Wirrel et al.[19] studied 250 patients with WS, and they were able to reveal the cause of WS in 161 (64.4 %), and in the majority of these patients (138) the diagnosis was based on only clinical assessment and MRI.

In our patients with pathological MRI results, brain malformation was the most common causative factor (21/55; 38%). This value is similar to the results of Poulat et al.[18] They found cerebral malformations and tuberous sclerosis in 15/40 (37.5%) patients with symptomatic WS. Hypoxia and ischemia were also comparable among our patients with WS (13/55; 24 %) and the population of children with WS of Poulat (15% hypoxic-ischemic encephalopathy and 2.5% periventricular leukomalacia).

But, when we examined separately the CP and non-CP groups, harmonizing with our hypothesis, the rate of hypoxia/ischemia was higher in the CP subgroup (12/39, 31%) than in the non-CP group (1/23, 4%). Surprisingly and contrary to our expectations, the rate of congenital brain malformations was higher in the non-CP group (11/23; 48%) than in the CP group (10/39; 26%). It is of interest that not only the prevalence of congenital brain malformations was higher in the non-CP group, but more hippocampal anomalies were revealed in this group as well (39.1% vs. 15.4%; p=0.035).

We studied separately the corpus callosum and the other pathological white matter anomalies. The rate of other pathological white matter findings was significantly higher in the CP than in the non-CP group (61.5% vs. 21.7%). This result correlates well with the pathomechanism of CP. The high rate of corpus callosum anomalies (18/62; 29%) mandates a more thorough investigation of the corpus callosum among patients with WS, especially in the CP group (14/39, 35.9%).

Normal MRI was found in 11.3% of our patients with WS (7/62). Compared to our results, Harini et al.**[14]** reported a higher rate (26.7%) of negative MRIs in children with WS. The background of this difference is unclear. One explanation can be the use of different quality MRI equipments and the role of radiologists with highly different clinical experience. When we separately examined the CP and non-CP populations, significant difference was revealed between them considering the negative MRI results (CP group 1/39, 2.6%; non-CP group 6/23, 26.1%). It is well known that in the minority of children with CP, no abnormality can be detected on MRI. In our CP population, normal MRI was found in only one patient. We believe that in this case genetic origin can be suspected, but it has not been confirmed, yet.

III.5.2. Clinical characteristics

The rate of *premature* infants in the CP group was almost double the rate of those in the non-CP group (21.7% vs. 41%). The premature rate in our CP group was similar to that study included patients with CP and with different types of epileptic syndromes.[20]

Our data did not reveal a difference in the age and in corrected age at the *onset of infantile spasms* between the CP and the non-CP groups, which may refer to the fact, that brain injuries causing CP do not influence the time of onset of West syndrome

We compared the distribution of the different CP *subtypes* in our CP group to a European CP population with epilepsy.[20] The rate of bilateral spastic CP was much higher in our population (36.6% vs. 80%), while the prevalence of unilateral spastic and dyskinetic CP was lower in our group (25.6% vs. 15% and 51.6% vs. 2.7%, respectively), and we did not find any patient with ataxic CP. This difference can be well explained with the fact that Sellier et al. studied a general CP population with several types of epilepsy (from the benign to the therapy-resistant epilepsies) while we included only the children with one of the most malignant epilepsy syndromes.

The prevalence of severe intellectual disability in our patients with WS was 35/58 (60%) which is only slightly higher than the findings of Riikonen[16] (75/147; 51%).

Considering the children in our CP group, 31/37 (84%) suffered from severe intellectual impairment. In an Australian population-based retrospective study, 45% of patients with CP had *intellectual disability* as well.[21] This large difference can be explained with the fact that we examined only children with WS and it supports our hypothesis about the especially unfavorable outcome of the CP subgroup with previous history of WS.

Hollung et al.[22] investigated the prevalence and severity of CP in Norway among children born between 1999 and 2010. The rate of those children, who were not *able to walk* (Gross Motor Function Classification System III-V[23]) ranged from 18.4 to 38.5%. In our CP group with WS, this proportion was 78%. This difference can be explained by the fact, that we examined a special CP population: our patients were affected not only by CP but WS as well, which is itself an epileptic encephalopathy with poor prognosis.

In the non-CP group, only two of our patients with neurodegenerative diseases were not able to walk. One of them had PEHO syndrome, which is a rare cause of WS. Riikonen et al.[16] found three cases in their population.

The rate of seizure-free patients was similar in the CP and non-CP groups (14%, 19%). Surprisingly, not only the prevalence of therapy-resistant *epilepsy* was higher in our non-CP group, but also the rate of seizure-free patients with medication was lower. An explanation can be that in our non-CP group we found a higher rate of cerebral anomalies (polymicrogyria, tuberous sclerosis, hippocampal anomalies etc.) and it is widely known, that the antiepileptic treatment of those epilepsies with these very severe congenital brain anomalies, is less favorable. Kaushik et al.[13] studied the factors influencing the favorable outcome of WS defined as a complete spasm cessation for at least 6 months without relapse or progression to other seizure types. They found that the age at onset, gender, time lag to treatment, presence of perinatal asphyxia or co-morbid CP did not affect the final outcome.

III.5.3. Conclusion

Our study investigated how the outcome of WS was influenced by the presence of CP. In the children with CP, pre-, perinatal hypoxia, ischemia, brain malformations,

cerebrovascular insults and CNS infections were the most common causative factors, while in the non-CP group the great majority of children had brain malformations and their epileptic prognosis was less favorable. Significant differences were found in MRI results between the CP and the non-CP groups. Interestingly, hippocampal anomalies were observed significantly more frequently in the non-CP group. Further research would be required to investigate the role of the hippocampus in WS. Corpus callosum anomalies were revealed in 29% of our patients with WS. The presence of WS in the medical history of a child with cerebral palsy indicates a more unfavorable prognosis considering the cognitive functions and walking ability.

IV. Clinical features of cerebral palsy. The role and relevance of cranial MRI in the investigation of causes of cerebral palsy

IV.1. Literature review

Cerebral palsy (CP) is a group of permanent, but not unchanging, disorders of movements and/or posture and of motor function originating from a lesion/abnormality/interference affecting the developing brain.[24] CP is an umbrella term. It involves patients with mild, almost invisible signs and those having very severe motor and cognitive disabilities. Its aetiology also varies over a wide range: several pre-, peri- and postnatal factors can be associated with CP and the role of certain genetic mutations becomes increasingly evident as well. [25] It can be accompanied by cognitive dysfunction, epilepsy, nutritional problems, vision and hearing problems.

The characteristic neuroimaging results in children with CP

As the Hungarian member of the „Surveillance of Cerebral Palsy in Europe" (SCPE) cooperation, we participated in the compilation of cranial MRI Classification System for cerebral palsy. The SCPE published a recommendation for the use of the **MRICS (MRI Classification System)** in 2017.[26] Based on MRI results, 5 main groups and few subgroups can be distinguished:

A. Maldevelopments
-A.1. Disorders of cortical formation (proliferation and/or migration and/or organisation
-A.2. Other maldevelopments (examples: holoprosencephaly Dandy-Walker malformation, corpus callosum agenesis, cerebellar hypoplasia)
B. Predominant white matter injury (WMI)
-B.1. Periventricular leukomalacia (mild/severe)
-B.2. Sequelae of intraventricular haemorrhage or periventricular haemorrhagic infarction
-B.3. Combination of PVL and IVH sequelae
C. Predominant grey matter injury (GMI)
-C.1. Basal ganglia/thalamus lesions (mild/moderate/severe)
-C.2. Cortico-subcortical lesions only (watershed lesions in parasagittal distribution/multicystic encephalomalacia) not covered under C3
-C.3. Arterial infarctions (middle cerebral artery/other)
D. Miscellaneous (examples: cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, haemorrhage not covered under B, brainstem lesions, calcifications)
E. Normal

IV.2. Aim-Hypothesis

We aimed

1/ to investigate the general characteristics of the Hungarian cerebral palsy population (in the covering area of the Department of Paediatrics, University of Pécs; determined as C23 region by SCPE: Baranya, Tolna and Somogy Counties and to compare these data to the international ones.

2/ to examine the usefulness of MRICS by the analysis of MRI findings of the patients mentioned above.

We hypothesised that the clinical and neuroimaging data of the examined Hungarian population would not differ from the published international results.

IV.3. Patients and method

IV.3.1. Patients

Department of Paediatrics, University of Pécs has a contractual relationship with SCPE from 2010. From 2016, since SCPE integrated into the Joint Research Centre, the JRC-SCPE cooperation has collected the data. Patients with CP born between 1990-2015 were involved from the South-West Hungary area (including Baranya, Somogy and Tolna counties).

IV.3.2. Method

The data were collected retrospectively from the electronic and paper-based databases of the hospital. The survey created by the SCPE research group was used.

- collected perinatal data: sex, birth weight, gestational age (prematurity was defined as birth before the 37th gestational week), method of birth, multiple birth, Apgar score at 5 minutes, convulsions within the first 72 hours, CP subtypes (bilateral spastic, unilateral spastic, dyskinetic or ataxic; in a mixed form, the dominant clinical feature was considered),
- Brain MRI results and their classification into five groups based on MRICS[26]. When more MRI scans were available, the findings of the latest was considered.
- values of Gross Motor Function Classification System (GMFCS)[23],
- values of Bimanual Fine Motor Function (BFMF)[27],
- intellectual impairment (normal IQ≥70, mild impairment IQ 50-69, moderate-severe impairment IQ≤49), presence of epilepsy, brain MRI results.

IV.3.3. Statistical method

IBM SPSS Statistics 24 (Armonk, NY: IBM Corp.) and RStudio (R.RStudio, Inc., Boston, MA) was used for statistical analysis. The level of significance was defined as 0.05.

IV.4. Results

418 children with CP were found in the investigated period. Those sixteen cases were excluded from the study, where both CP subtype and MRI findings were missing. 402 children with CP were eligible to enrol in the study. In 145 cases MRI results were not available. 257/402 (64%) patients were involved in the MRI assessment study.

IV.4.1. Clinical characteristics of the total CP population

We examined the general characteristics of the CP population and the differences were tested between the populations with and without MRI.

IV.4.1.1. Perinatal data

Male dominance characterised our population (60.4%) both among preterm and term babies (68% and 58%) and no significant difference was revealed in the sex distribution of preterm and term infants (p=0.421). The rate of premature infants (born before 37th gestational week) was 46.5%. Birth weight was < 2500 g in 51.1% of the children. Birthweights and gestational ages were significantly lower in the group without an MRI. Those patients, whose MRI scans were available, had seizures more frequently in the first 72 hours. The highest premature rate was observed in bilateral spastic CP (53.2%).

IV.4.1.2. CP subtypes

Spastic CP was the most common in our patients with 86.6% (60.2% bilateral, 26.4% unilateral), the rate of dyskinetic and ataxic CP was 2.5% and 10.9 %, respectively. We found, that focal neurological signs seemed to be the most alarming sign for the paediatricians to order MRI examination, as 80.2% of the patients with unilateral spastic CP had had MRI.

IV.4.1.3. GMFCS, BFMF and IQ values

No significant differences were found in the distribution of GMFCS, BFMF scores and IQ values between the groups with and without MRI. 36.8% of our patients received the worst score (5) on GMFCS and 29.9 % on BFMF scales. 53.7% of our population had IQ≤49.

IV.4.1.4. Epilepsy

57.1% of our patients had had epilepsy. The rate of epilepsy was higher in the group with an available MRI. The rate of epilepsy was significantly higher in those patients, who had already had convulsions in their first 72 hours (35/176, 19.9% vs. 14/133, 10.5%; Chi-square test, p=0.026).

IV.4.2. Cranial MRI patterns according to MRICS in relation to perinatal and functional factors

65.4% of the MRIs were performed at the age of 2 years or later. White matter injuries (B) were the most frequent abnormalities in 35.4% of patients. Maldevelopments (A) and grey matter injuries (C) were similarly common; they occurred in 18.7 % and 19.8% of the cases, respectively. 12.5% of the patients were classified to the miscellaneous (D) group. No abnormality was revealed by MRI (E) in 13.6% *(Table 4)*.

	Maldevelopment		WMI		GMI		Miscellaneous		Normal		TOTAL		p-value
	48 (18.7%)		91 (35.4%)		51 (19.8%)		32 (12.5%)		35 (13.6%)		257		
	N	%	N	%	N	%	N	%	N	%	N	%	
Sex													0.237
• male	25	*52.1*	56	*61.5*	24	*47.1*	20	*62.5*	24	*68.6*	149	*58*	
• female	23	*47.9*	35	*38.5*	27	*52.9*	12	*37.5*	11	*31.4*	108	*42*	
Birthweight (g)													<0.001
• 2500≤	35	*79.5*	27	*32.1*	37	*77.1*	19	*61.3*	25	*78.1*	143	*59.8*	
• 1500≤ BW <2500	6	*13.6*	19	*22.6*	9	*18.8*	9	*29*	5	*15.6*	48	*20.1*	
• 1500>	3	*6.8*	38	*45.2*	2	*4.2*	3	*9.7*	2	*6.3*	48	*20.1*	
Gestational age (weeks)													<0.001
• 36<	36	*83.7*	26	*31*	40	*80*	19	*63.3*	24	*77.4*	145	*60.9*	
• 28-36	7	*16.3*	37	*44*	10	*20*	9	*30*	6	*19.4*	69	*29*	
• 28>	0	*0*	21	*25*	0	*0*	2	*6.7*	1	*3.2*	24	*10.1*	
Apgar													0.5479
• 7-10	33	*91.7*	65	*86.7*	33	*80.5*	20	*90.9*	25	*89.3*	176	*87.1*	
• 4-6	2	*5.6*	9	*12*	6	*14.6*	2	*9.1*	1	*3.6*	20	*9.9*	
• 0-3	1	*2.8*	1	*1.3*	2	*4.9*	0	*0*	2	*7.1*	6	*3*	
Method of delivery													0.100
• vaginal	34	*72.3*	44	*50*	30	*58.8*	20	*64.5*	23	*67.6*	151	*60.2*	
• caesarean section	13	*27.7*	44	*50*	21	*41.2*	11	*35.5*	11	*32.4*	100	*39.8*	
Plurality													0.003
• singleton	46	*95.8*	76	*83.5*	51	*100*	31	*96.9*	33	*94.3*	237	*92.2*	
• multiple	2	*4.2*	15	*16.5*	0	*0*	1	*3.1*	2	*5.7*	20	*7.8*	
Neonatal seizures													0.13
• yes	3	*8.8*	13	*16.5*	14	*31.8*	4	*16*	5	*19.2*	39	*18.8*	
• no	31	*91.2*	66	*83.5*	30	*68.2*	21	*84*	21	*80.8*	169	*81.3*	

Table 4 MRI results in relation to perinatal factors

(Abbreviations: WMI, white matter injury, GMI, grey matter injury; BW, birthweight)

IV.4.2.1. Perinatal data and the MRICS

Significant differences were revealed in relation to MRI subcategories in the following: birthweight, gestational age and plurality categories.

Birthweight: 59.4% of babies born <2500 g had WMI, and 79.2% of those babies whose birth weight was below 1500 g suffered WMI. Maldevelopments and GMIs mainly affected children born with normal birth weight. 78.1% of patients with normal MRI had a normal birth weight.

Gestational age: The distribution of gestational age categories correlated well with those of birthweight categories. The prematurity rate was the highest in patients with WMI (69%). 83.7 % and 80% of children with maldevelopment and GMI were born at term.

We found no significant difference in the distribution of sexes and Apgar score categories, methods of delivery, neonatal seizures concerning MRI subcategories.

Neonatal seizures: Convulsions within the first 72 hours occurred most frequently (31.8%) in patients with GMI. This rate was also considerable (19.2%) in the group with normal MRI *(Table 4)*.

IV.4.2.2. CP subtypes

WMI was found in 39.6% of children with bilateral spastic CP. Those children who had GMI, 64.7% had unilateral spastic CP. These patients constituted 38.8% (33/85) of all patients with unilateral spastic CP. We found normal MRI in 16/35 cases with bilateral and 13/35 cases with unilateral spastic CP *(Table 5)*.

IV.4.2.3. GMFCS, BFMF and IQ

GMFCS and BFMF scores were the most favourable in the groups with normal MRI and with GMI; in every category, the rate of scores I-II. was more than 60 %. The patients with maldevelopments and those with miscellaneous findings scored worst; in more than 65% of patients received scores III-V.

Intellectual impairment was the most severe in patients with maldevelopments; 74% of them had IQ≤49. The rate of normal intellectual ability was the highest in the group with GMI and with normal MRI (56.8% and 41.9 %, respectively) *(Table 5)*.

IV.4.2.4. Epilepsy

The prevalence of epilepsy was above 60% in every group with abnormal MRI (A-B-C-D). The highest rate was observed in the miscellaneous group *(Table 5)*.

IV.5 Discussion

In our study, we examined clinical characteristics and cranial MRI results of patients with CP from our CP register which covers the population of South-West Hungary. The MRI classification system (MRICS) published by SCPE in 2017 was used to evaluate the MRI results. As far as we know, this is the first research investigating a Hungarian population with all types of CP. Hollódy and Szőts[28] had already studied Hungarian patients but with only bilateral spastic CP born between 1975-86.

IV.5.1. Characteristics of our CP population compared to the international data

A male predominance was observed in our population (60.4%). The rate of male sex was similar in the Reid's study from Australia (59.1%)[29], Himmelmann's studies from Sweden (60% and 60%)[30; 31] and Benini's research from Canada (54%).[32]

	Maldevelop-ment		WMI		GMI		Miscella-neous		Normal		TOTAL		p-value
	48 (18.7%)		91 (35.4%)		51 (19.8%)		32 (12.5%)		35 (13.6%)		257		
	N	%	N	%	N	%	N	%	N	%	N	%	
CP subtypes													0.0005
• bilateral spastic	32	*66.7*	57	*62.6*	15	*29.4*	24	*75*	16	*45.7*	144	*56*	
• unilateral spastic	8	*16.7*	28	*30.8*	33	*64.7*	3	*9.4*	13	*37.1*	85	*33.1*	
• dyskinetic	1	*2.1*	1	*1.1*	3	*5.9*	1	*3.1*	0	*0*	6	*2.3*	
• ataxic	7	*14.6*	5	*5.5*	0	*0*	4	*12.5*	6	*17.1*	22	*8.6*	
GMFCS													0.001
• 1-2	15	*31.9*	44	*48.9*	32	*65.3*	9	*30*	22	*62.9*	122	*48.6*	
• 3-5	32	*68.1*	46	*51.1*	17	*34.7*	21	*70*	13	*37.1*	129	*51.4*	
BFMF													<0.001
• 1-2	16	*34*	40	*45.5*	30	*60*	8	*26.7*	25	*73.5*	119	*47.8*	
• 3-5	31	*66*	48	*54.5*	20	*40*	22	*73.3*	9	*26.5*	130	*52.2*	
Intellectual impairment													<0.001
• IQ ≥ 70	8	*20.5*	26	*32.9*	21	*56.8*	3	*10.7*	13	*41.9*	71	*33.2*	
• IQ 50-69	2	*5.1*	13	*16.5*	6	*16.2*	2	*7.1*	5	*16.1*	28	*13.1*	
• IQ ≤ 49	29	*74.4*	40	*50.6*	10	*27*	23	*82.1*	13	*41.9*	115	*53.7*	
Epilepsy													0.001
• yes	33	*70.2*	56	*62.9*	38	*77.6*	26	*81.3*	14	*40*	167	*66.3*	
• no	14	*29.8*	33	*37.1*	11	*22.4*	6	*18.8*	21	*60*	85	*33.7*	

Table 5 *MRI results in relation to CP subtypes, functional scores and epilepsy (Abbreviations: CP, cerebral palsy; MRI, magnetic resonance imaging; GMFCS, Gross Motor Function Classification System; BFMF, Bimanual Fine Motor Function; WMI, white matter injury; GMI, grey matter injury; IQ, intelligence quotient)*

As far as we know, there has been no correct explanation for this sex difference, it can possibly be attributed to the higher susceptibility of male fetuses. Interestingly, Himmelmann[33] found a female predominance earlier among term infants, while in the preterm group, a male predominance was observed. Reid et al.[34] also found the overrepresentation of males in preterm live births. We did not find a difference in the gender rate among preterm and term infants.

More than half of our CP patients were born with normal birth weight (>2500 g, 51.1 %) and at term (>36 gestational weeks, 53.5%). These data correlate well with the published international data[35]. Bax et al.[36] in a European Cerebral Palsy Study (2006) found that 54.5% of children with CP were born at term.

The rate of caesarean section in our CP population is 39.3%, but it is not significantly higher than in the Hungarian general population (39%) at present, it must be noted, however, that this rate was only 10% in 1990. However, the rate of caesarean section has globally increased from 12.1% (2000) to 21.1% (2015) in 15 years[37]. Among CP patients, Bax et al.[36] observed the same proportion (39.3%) of caesarean section as well.

In our CP population, the majority (87.1%) of patients were born with Apgar 7-10. This rate is very similar to the proportion of Reid's study[29] (82%); however, considering the high rate of prematurity and caesarean section, the given Apgar scores should be carefully assessed.

Convulsions in the first 72 hours, affected 15.8 % of our patients. Reid et al.[29] found a higher rate of seizures in neonatal age (31.59%), probably this difference may originate from the different duration of observation periods (first three days vs. neonatal period).

The rate of spastic CP (86.6%) was almost the same than in the article published by SCPE collaboration group (85.75%)[38]. Children born between 1976 and 1990 from 13 centres were included. Bax[36] found 79.2% rate (birth years 1996-1999,) Himmelmann[30] revealed 79% rate (2003-2006). Interestingly, the rate of patient with dyskinetic CP was lower in our study compared to the SCPE data[38] (6.5% vs. 2.5%), while the proportion of children with ataxic CP was higher (4.3% vs. 10.9%) despite the fact that all examined children were older than 4 years and progressive neurodegenerative diseases were excluded.

Asymmetry is a very alarming and usually easily recognisable neurological sign. This can explain the fact that in our study, MRI was performed most frequently in the unilateral spastic CP group (80.2%). Interestingly, Robinson et al.[39] found the opposite; children with hemiplegia or monoplegia were less likely to have had an MRI (59.5%). The lower rate of MRI in these cases considering Robinson's study may be explained maybe with the involvement of not only hemiplegic but also monoplegic patients.

Comparing the GMFCS scores in our research to the Australian study (Reid 1999-2006)[29], we have to conclude, that the rate of GMFCS III-V. scores were reasonably higher (51.2 % vs. 38%) in our population. Hollung et al.[22] investigated cerebral palsy in Norway among children born 1999 to 2010; they found that 65-92% of children had GMFCS I-II. These diverse data can be explained by the different study period; we reviewed a remarkably longer (26 vs. 7 and 11 years) period from 1990 to 2015 and perinatal intensive care has developed considerably since 1990.

Considering BFMF scores, 48.7% of our patients received BFMF I-II. This value is only slightly lower than those found in a study from Norway[40] with children born 1996-1998 (53%). In this study, GMFCS I-II. scores were characteristic for 55% of patients.

In a population-based retrospective study, Reid reported that 45% of children with CP had intellectual disability[21]. The higher observed rate (67.6%) of intellectual disability in our examined population correlates well with the more severe motor impairment.

IV.5.2. The classification of MRI results in patients with CP

According to the latest guideline, at least one MRI examination is recommended in every patient with CP after the age of two years when the myelinisation of the brain is almost complete. The MRI findings may help to understand the aetiology of CP. Several classification systems exist considering the MRI findings of CP patients, the harmonisation of these systems is challenging [26; 29; 32; 41; 42].
In 86.4% of our patients, abnormalities were found on MRI. Korzeniewski et al.[41] reviewed 20 studies and found, that 80.1% (55.1-100%) of patients demonstrated image abnormalities. Reid et al.[29] found normal MRI in almost the same proportion (13% vs. 13.6%) of their patients compared to our results. In their study, the rate of WMI (45%) seemed to be higher, and the rate of maldevelopment (10%) was lower than our results. In Benini's research[32], the rate of normal MRI was much higher (29%). The great discrepancy between Benini's and our results considering the rate of normal MRIs can probably be explained with the fact that in Benini's study patients underwent 1.5T MRI between 1999 and 2002, while our patients were examined by 1.5 and 3 T MRI till 2015.

IV.5.3. Evaluation of perinatal data in relation to the MRICS

Distribution of birthweight and gestational age can well represent, that WMI was found mainly in the prematurity/low birthweight category while term newborns/ newborns with normal birthweight were more often affected by GMI or maldevelopment. Patients with normal MRI were usually born with normal birth weight and at term.

IV.5.4. CP subtypes and the MRICS

Unilateral spastic CP type was mostly associated with GMI (33/85). In these cases, the one-sided occlusion of the arteria cerebri media was the most common MRI finding. Bilateral spastic CP was most frequently caused by WMI (57/144); origin from bilateral periventricular leukomalacia seemed to be the most common.

IV.5.5. Functional scores and the MRICS

Interestingly, not only the patients with normal MRI seemed to have better GMFCS, BFMF and IQ scores, but also those with GMI. Numata et al.[42] investigated 86 patients born at term with spastic diplegia. Surprisingly, they revealed no difference in the frequency of intellectual impairment between groups with normal and abnormal MRI findings and over 50% of their patients with normal MRI had an intellectual disability. That is why they referred to negative MRI results as "yet undetected abnormalities".

IV.5.6. Epilepsy and the MRICS

It should be highlighted, that our study found a high prevalence rate of epilepsy. More than 60% of patients were affected by epilepsy in every group with abnormal MRI. The high prevalence can be explained with the fact that in our survey we investigated whether the children had ever had epilepsy in their childhood, while the others revealed the epileptic status of their patients in a limited time period [43-45].

V. Summary of the novel findings

V.1. Differential diagnosis of neonatal and infantile paroxysmal events

Neonatal and infantile paroxysmal events can usually be diagnosed correctly with video-EEG. However, knowing the semiology of benign phenomena (characteristic for a certain age group) and epileptic attacks can be helpful in the differential diagnosis. Our research proved that the correct recognition of these events increases proportionally with experience and professional qualification, thereby highlighting the importance of proper education. Previous education of parent about epilepsy seems to have on impact as well, as their results were better than those of first-year medical students. The characteristic appearance of jitteriness, benign neonatal sleep myoclonus or infantile masturbation and the knowing of circumstances are helpful for making the correct diagnosis and avoiding unnecessary (even invasive) investigations. Home-made video recordings about suspicious phenomena can help medical doctors with the decision. First of all, we wanted to call the attention of the paediatric general practitioners to the importance of correct evaluation of benign movements. It is beneficial, that the recognition of paroxysmal events was similar given by neonatologists working at neonatal intensive care units and paediatric neurologists that provide consultations to their colleagues or treat the infants later.

V.2. Aetiology and prognosis of patients with West syndrome. The occurrence of cerebral palsy in patients with West syndrome

To the best of our knowledge, this is the first study which compares patients with West syndrome grouped not only based on their epileptic state but also according to their motor function.

We investigated patients with only West syndrome and patients with West syndrome and co-occurred cerebral palsy separately. Our data showed differences between the two groups in the occurrence of brain malformations, hippocampal anomalies and other (corpus callosum disorder excluded) white matter disorders. Brain malformations and hippocampal anomalies were present more often in non-CP patients with West syndrome than the CP patients. In this research- similarly to international data- a relatively high rate of patients with West syndrome had negative MRI. Further investigations would be necessary to provide better evidence.

Our study has been the first to describe that the clinical course of epilepsy in patients with cerebral palsy and West syndrome is more favourable than that of patients with West syndrome only. However, patients with West syndrome and co-occurred cerebral palsy have worse prognosis considering not only their motor function but their cognitive function as well.

V.3. Clinical characteristics of cerebral palsy. The role and relevance of cranial MRI in the investigation of causes of cerebral palsy

Unfortunately, no national Hungarian CP registry exists. The Cerebral Palsy Register of South-West Hungary (Baranya, Tolna, Somogy Counties) was started and has been working as part of an international collaboration. Based on the data of our registry, that clinical features of the Hungarian patients with cerebral palsy do not differ from international data considering male predominance, average birth weight, rate of prematurity, occurrence of caesarian section and Apgar scores.

Regarding CP subtypes, the spastic type was the most common in our database. Not only the more severe forms of cerebral palsy (GMFCS, BFMF III-V) were more common in our register compared to international data, but presumably because of this, the intellectual and epileptic state of these patients were also found to be worse as well. A possible explanation of the more unfavourable results can be that we involved patients with CP born in a relatively long time interval (born 1990-2015). We expect that this difference will disappear with the improvement of perinatal care in the future.

We proved, that the MRICS (MRI Classification System) created by SCPE (Surveillance of Cerebral Palsy in Europe, with our participation) is helpful and provides a unified language in the investigation of CP aetiology. White matter injuries were found more frequently in premature infants, while grey matter injuries were more common in mature infants.

The rate of normal MRI (13.6%) was similar to international data. The gross-, fine-motor and cognitive functions of patients with normal MRI were as good as those of patients with grey matter injuries. In the future, further (mainly genetic) tests may help identify the possible causes of cerebral palsy in children with normal MRI.

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VII. Publications related to this thesis

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Nagy E, Farkas N, Hollódy K. Paroxysmalis jelenségek megítélése az újszülött- és csecsemőkorban. Ideggyógyászati Szemle 2018; 71(9–10):313–319. **[IF: 0.113]**

Nagy E, Péter I, Hollódy K. Kettős patológia: cerebralis paresis és plexus brachialis laesio együttes előfordulása. Gyermekgyógyászat, 2018; 69(3): 131-132.

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Nagy E, Farkas N, Hollódy K. Does co-occurred cerebral palsy change the prognosis of West syndrome? Neuropediatrics [accepted for publication] **[IF: 1.654]** (2018)

Citable abstract related to this thesis

Hollódy K, **Nagy E**, Major A, Farkas N. Epileptic seizure or not? Proportion of correct judgement among medical doctors, medical students and parents based only on a video recording of a paroxysmal event. EPNS Conference, Lyon, France, 2017. Eur J Paediatr Neurol 2017; 21, e167 - e168. **[IF 2.362]**

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Nagy E, Major A, Farkas N, Hollódy K. Újszülött- és fiatal csecsemőkori mozgásjelenségek megítélése. Felismerhető-e az epilepszia csak egy videófelvétel megtekintése alapján? Magyar Gyermekneurológiai Társaság Kongresszusa, Pécs, 2017.

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Nagy E, Farkas N, Hollódy K. The determination of etiological factors by neuroimaging in children with West syndrome and concomitant cerebral palsy. Poster. European Academy of Childhood Disability Congress, Paris, 2019.

Hollódy K, **Nagy E**. Girls with Rett syndrome grow into adults. Poster. European Academy of Childhood Disability Congress, Paris, 2019.

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