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ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

CLINICAL FEATURES, PREVALENCE, RISK FACTORS AND PROGNOSIS OF EPILEPSY IN CHILDREN WITH CEREBRAL PALSY

Speciality: 3223.01 – Nervous diseases

Field of science: Medicine

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GENERAL DESCRIPTION OF WORK

The urgency of the problem. Epilepsy is one of the most common severe diseases of the nervous system, which has a significant impact on both the quality of life of the patient and his family members. The prevalence among the adult population in developed countries is 5.2 /1000 people , in developing countries - 8.7 /1000 people in urban areas population, the prevalence among children is 3.2-5.5/1,000 people in developed countries and 3.6-44/1,000 people in developing countries.[1] According to 2004 data, in Azerbaijan, the incidence of epilepsy in the population among children under 14 years was 36.7 per 100,000 children, and the prevalence was 1.3 per 1,000 children [2.] One of the main causes of symptomatic epilepsy is perinatal brain damage. Structural damage to the central nervous system in many cases is so significant that it leads to the formation of cerebral palsy (CP). Cerebral palsy is a nervous system complex development disease of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[3] Cerebral palsy is the most common cause of physical disability in childhood, averaging 2-2.5 cases per 1,000 people in high-income countries. Epilepsy is one of the most common problems in children with cerebral palsy and occurs in about 25-45% of cases.[4] The estimated prevalence of seizures and epilepsy in cerebral palsy varies greatly depending on the underlying pathology and etiology.

1. Beghi E.The Epidemiology of Epilepsy. Neuroepidemiology 2020;54:185-191. doi: 10.1159/000503831
2. Ахмедов Т.М. // Распространённость эпилепсии у детей в республике Азербайджан и перспектива развития эпилептологической службы //2013. с.109
3. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson B. A report: the definition and classification of cerebral palsy April 2006 //Dev Med Child Neurol 2007Suppl 109:8–14
4. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy.//Pediatrics 2012;130:e1285-312.

The problem of the relationship between these diseases is quite relevant in pediatric neurology. Epilepsy in children with cerebral palsy is characterized by an earlier onset, a low frequency of generalized seizures, as well as the widespread use of drugs of the second choice group in therapy (vigabatrin, lamotrigine, topiramate, clonazepam), polytherapy, and pharmacoresistance.[5] Cerebral palsy and epilepsy, being common causes of childhood disability, have negative social consequences, contributing to a decrease in the quality of life of patients and their families. Lack of information about risk factors, clinical features and the course of the epileptic syndrome in cerebral palsy greatly complicates the implementation of rehabilitation measures and often leads to an unfavorable course of epilepsy. Thus, children with cerebral palsy have a wide range of forms of epilepsy: both severe forms with an early onset, mental retardation, frequent seizures (West syndrome), and benign forms with a later onset, rare seizures and normal intelligence. To date, the literature remains insufficiently covered questions about the frequency of epileptic syndrome in cerebral palsy, the factors contributing to its increase, the age of onset of convulsive seizures, the effect of cerebral palsy on the manifestation of epilepsy, the prognosis of its course and treatment tactics. These circumstances indicate the relevance of studying epilepsy in patients with cerebral palsy and require further researches.

In Azerbaijan, over the past two decades, special attention has been paid to the study of various aspects of epilepsy.[6] Thus, the epidemiology of epilepsy was revealed in various regions and cities of the republic, the quality of life of patients with epilepsy, and the problem of epilepsy in pregnant women was also studied. However, work on the study of epilepsy in patients with cerebral palsy has not previously been carried out.

5. Pavone P, Gulizia C, Le Pira A, et al. Cerebral Palsy and Epilepsy in Children: Clinical Perspectives on a Common Comorbidity. Children (Basel). 2020;8(1):16. doi:10.3390/children8010016
6. Mahalov Ş.I. Epilepsiya / Mahalov Ş.I. - Bakı: Oğuz Eli ,-2015, -149 s.

Object and subject of research. The object of the study were patients with cerebral palsy, who are on inpatient or outpatient treatment.

Purpose of the study. To study clinical features, prevalence, risk factors, prognosis of a disease course, development of practical recommendations aimed at improving the early diagnosis and adequate management of epilepsy in children with cerebral palsy.

Research objectives.:

1. To analyze the prevalence and characteristics of epilepsy in children with cerebral palsy based on the materials of the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku for 2013-2017 years.
2. To establish the features of the course (age of onset, the frequency and nature of seizures),prevalence and prognosis of epilepsy in various forms of cerebral palsy.
3. To study the most probable etiological factors (heredity, pathology of the perinatal period, especially brain malformations) leading to epilepsy in cerebral palsy.
4. To give a comprehensive clinical and electrophysiological characteristics of cerebral palsy with epilepsy.
5. Evaluate the impact of epilepsy on the quality of life of children with cerebral palsy.
6. To determine the adequacy of antiepileptic therapy for various forms of cerebral palsy, as well as the effectiveness of mono and polytherapy.

Research methods. Dynamic monitoring of children with cerebral palsy and cerebral palsy with epilepsy. It was a clinical study with prospective-retrospective design.

Provisions for defense:

– Epilepsy often accompanies cerebral palsy. In patients with cerebral palsy, symptomatic epilepsy is manifested a lot by focal and secondarily generalized tonic-clonic seizures with a debut of up to 2 years. Epilepsy is more likely to develop in patients with more severe motor impairment. In particular, the quadriplegic form of cerebral palsy is predominant in cerebral

palsy and epilepsy combination.

- Neonatal seizures, infectious diseases in the mother during pregnancy, the presence of epilepsy in the family history and epileptiform activity on the EEG are associated with a high risk of developing epilepsy in patients with cerebral palsy.
- Epilepsy reduces the quality of life of patients with cerebral palsy.
- Epileptic seizures in the presence of cerebral palsy are difficult to manage, in many cases several antiepileptic drugs are used (polytherapy).

Scientific novelty of research. The prevalence of epilepsy in children with cerebral palsy in the Neurological Department of the Educational Therapeutic Clinic of the AMU and Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku was determined. Prognostic significant risk factors for the development of epilepsy in this category of patients, pathology features of the pre- and perinatal period, and hereditary predisposition were identified. The semiological structure of epilepsy was studied depending on the age of the onset of seizures and its prognosis. Clinical and electroencephalographic correlations have been established depending on the form of cerebral palsy, type of seizures, structural changes in the brain according to neuroimaging (CT, MRI), age of the child and seizures onset. The feasibility of a comprehensive clinical and neurophysiological approach to diagnosis, the significance of risk factors and prognosis of cerebral palsy with epilepsy are assessed. And also, the epilepsy impact on the quality of life of patients with cerebral palsy was studied.

The theoretical and practical significance of the work. In this study, the course and clinical features of epilepsy in patients with cerebral palsy were studied. Identified risk factors for the development of epilepsy in patients with CP may be useful in predicting the onset of epilepsy, since knowledge of such factors may allow for more careful monitoring of these patients, for example, more frequent assessment in an outpatient clinic , informing families about seizures, and early detection of epileptic seizures. The use of a specific questionnaire

"Quality of Life in Children with Cerebral Palsy" (CP QOL) to evaluate the quality of life in children with cerebral palsy has great practical importance and also allows us to analyze the effectiveness of therapeutic interventions in relation to the quality of life of patients.

Early detection of epilepsy in CP patients, dynamic observation by a neurologist, as well as the appointment of timely treatment with antiepileptic drugs can help improve the prognosis of the disease in general.

Study approbation : The materials of the dissertation work were presented in person and discussed at the symposium of the participants of the Conference "Actual problems of Neurology" (Nakhichevan, June 2019), the 13th European Congress of Pediatric Neurology (Athens, Greece, September, 2019) , at the 17th Eurasian and World Turkic Pediatric Congress (UNPSTR) (Baku, September, 2019), the National Congress "Actual Issues of Perinatal Neurology" (Kyiv, October 2019), at the 4th International Neurological Congress of Turkic-speaking Countries (Baku, December 2019), at a conference dedicated to the 90th anniversary of the Azerbaijan Medical University (Baku, December 2020) at a conference dedicated to Actual Problems of Medicine in Azerbaijan (Baku, Baku) Baku, April 2021), 14th European Congress of Pediatric Neurology (Glasgow, UK, May 2022).

The initial approbation of the work was carried out at a general interdepartmental meeting of the Department of Neurology, the Department of Children's Diseases, the Department of Internal Diseases and the Department of Psychiatry (Protocol No. 1 dated 24.02.2022). Dissertation discussion was held at a meeting of the Approbation Commission of the Dissertation Council BFD 4.07 at the Azerbaijan Medical University (Protocol No. 1 dated 20.06.2022)

Implementation in practice: The scientific and practical results obtained in the course of the study were introduced into practice at the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova , at the Neurological Department of the Educational Therapeutic Clinic of the Azerbaijan Medical University, at the Scientific-Research Pediatrics Institute named after K. Farajova and children's polyclinics in Baku.

The name of organization where dissertation were carried

out. The dissertation work was performed at the Department of Neurology in Educational and Therapeutic Clinic of the AMU and at the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku.

Publications. 15 scientific papers were published on research topic, among them 9 are journal articles, 3 of which were published in foreign peer-reviewed scientific journals.

The volume and structure of the dissertation. The dissertation is presented on 172 pages of computer text (184.896 characters), contains 15 figures and 20 tables, consists of a list of abbreviations, an introduction (11.511 characters), a literature review (60.471 characters), material and methods (15.517 characters) chapters of own research results (11.327+25.562+12.808+13.267 characters), a conclusion, conclusions, practical recommendations (34.407 characters), applications and a list of references. The literature references include 183 sources, made up of 16 works by Azerbaijani, 9 Russian and 158 foreign authors.

MATERİALS AND METHODS

This retrospective-prospective study involved 160 patients with cerebral palsy who were treated at the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku and the Neurological Department of the Teaching and Therapeutic Clinic of the AMU in Baku from 2018 to 2021 years. Epileptic seizures were observed in 110 children with cerebral palsy, 50 children had CP without epileptic seizures. Gender distribution: 110 boys and 50 girls.

In addition, a retrospective study was conducted, where the medical records of children diagnosed with cerebral palsy and epilepsy from the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku for 2013-2017 were analyzed.

Demographic information was recorded using a detailed history collected from parents, including birth weight , gestational age , neonatal seizures , parental consanguinity , and family history of epilepsy.

The diagnosis of cerebral palsy was established in accordance with the recommendations on the modern classification of cerebral palsy and the International Classification of Diseases 10th revision (ICD-10) [3]. The following forms of cerebral palsy were identified: spastic hemiplegia, spastic diplegia, spastic quadriplegia, hyperkinetic, ataxic and mixed. The Gross Motor Function Classification System (GMFCS) was used to determine the severity of motor impairment in children.[7] This system (GMFCS) was developed to classify functional mobility in children diagnosed with cerebral palsy and consists of five levels ranging from I, which includes children with minimal or no dysfunction, to V, including children who completely mobile dependent and need assistance with movement.[8] The main perinatal factors by which we classified patients were: prematurity (children born before the 37th week of pregnancy), birth weight (less or more than 2500 g), head size (normocrania, microcrania or macrocrania), gestational age (term babies - from 38 to 41 weeks, premature - from 30 to 37 weeks, extremely premature - less than 30 weeks), type of delivery (natural childbirth, caesarean section). The definition of epilepsy applies to two or more unprovoked seizures.[9]

The quality of life was assessed using a specific questionnaire for children with CP "Quality of life in children with cerebral palsy" (CP QOL-Child). We used the parent/caregiver version, each questionnaire contains 66 questions in the following areas: social wellbeing and acceptance, feelings about functioning, participation and physical health, emotional wellbeing and self-esteem , access to services, pain and impact of disability , family health.

7. PalisanoRJ , Rosenbaum PL, , Bartlett DJ, Galuppi BE, Russell DJ. Development of the Gross Motor Function Classification System for cerebral palsy. //Dev Med Child Neurol. 2008;50(4):249-253.
8. Waters E, Davis E, Boyd R, et al. Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-Child) Manual. Melbourne: Deakin University; 2006.
9. Scheffer I.E., Berkovic S., Meletti S., Connolly M.B., French J., Guilhoto L., Hirsch E., Jain S., Mathern G.W., Moshé S.L., et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology //Epilepsia. 2017;58:512–521. doi: 10.1111/epi.13709.

All patients underwent routine electroencephalography (EEG) using a Neuron-Spectrum device, 16 channels with electrodes applied according to the international 10/20 system. In some cases, when it was difficult to diagnose the type of seizures, a video-EEG monitoring was performed. To detect latent epileptiform activity, EEG recordings were obtained during and after sleep deprivation. The type of epileptic seizures was determined according to the classification of the International League Against Epilepsy.

All patients underwent head magnetic resonance imaging (MRI) or computed tomography (CT), the results were described by radiologists.

The study was approved by the ethics committee of the Azerbaijan Medical University (protocol No. 11 dated December 29, 2019).

Statistical processing. The obtained quantitative and qualitative data were subjected to statistical processing by methods of medical statistics: variational (Student-Bonferroni, U-Mann-Whitney, H-Kruskal-Wallis), dispersion (ANOVA test), discriminant (χ2-Pearson, odds ratio) analyses. All calculations were carried out on a spreadsheet MS EXCEL-2019 and in the statistical package IBM Statistics SPSS-26.

RESULTS OF THE STUDY

The study included 160 patients with cerebral palsy. Among our patients males predominated (66.3%). The average age of the children was 4.65 ± 3.38. The mean age of the mother at birth was 25.47±4.9. 20% of our patients were born from a consanguineous marriage (marriage between first cousins). During pregnancy 34.4% of mothers suffered infectious diseases, most of which were TORCH infections (toxoplasmosis, rubella, cytomegalovirus and herpetic infections). As for pregnancy complications, it should be noted that 22.5% of mothers had preeclampsia in pregnancy, and 25.6% of mothers received drugs for a certain disease (anticoagulants, antiepileptics, antivirals, drugs to maintain pregnancy). 75.6 % of children were born naturally, 24.4% by caesarean section. 39.4% of patients were born prematurely. Regarding birth weight, 32.5% of children were born weighting <2500 g. It should be noted that 90.6% of patients had a history of hypoxic-

ischemic injury of varying degrees. In 3.8% of cases, multiple pregnancy was observed.

To study the impact of epilepsy on the course of cerebral palsy, two groups were created and compared. Group 1 consisted of 110 (68.7%) patients with cerebral palsy and epilepsy, and group 2 consisted of 50 (31.3%) patients with cerebral palsy, the age of the children ranged from 1 to 14 years. In the main group, 35 (31.8%) patients were girls and 75 (68.2%) boys, the average age of children was 4.8 ± 3.4 years. In the control group, 35 (70%) of 50 patients were boys and 15 (30%) girls; the average age of the children was 4.3 ± 3.4 years. There was no significant difference in the distribution of age and sex in the groups ($p = 0.492$ and $p = 0.818$, respectively).

In addition, there was no statistically significant difference between the two groups in terms of the average age of the mother at the delivery (25.4 ± 4.5 years in patients with CP and epilepsy; 25.4 ± 5.6 years in CP patients without epilepsy) ($p = 0.953$).

In both groups, there was a predominance of patients with spastic forms of cerebral palsy. Patients in the main group had the following types of cerebral palsy: quadriplegia in 59 (53.7%) , followed by hemiplegia in 25 (22.7%) , diplegia in 16 (14.5%) , ataxic in 7 (6.4%) and hyperkinetic in 3 (2.7%). In the control group: quadriplegia in 25 (50%) , hemiplegia in 15 (30%) , diplegia in 3 (6%) , ataxic in 3 (6%) and hyperkinetic in 4 (8%) patients.

In the course of our research, we assessed gross motor functions using the GMFCS scale and studied their relationship with epilepsy in CP children. It is worth noting that patients in the group with epilepsy compared to those without epilepsy, showed more GMFCS IV and GMFCS V levels .On the other side in the control group , more often GMFCS III level was observed ($p < 0.001$).

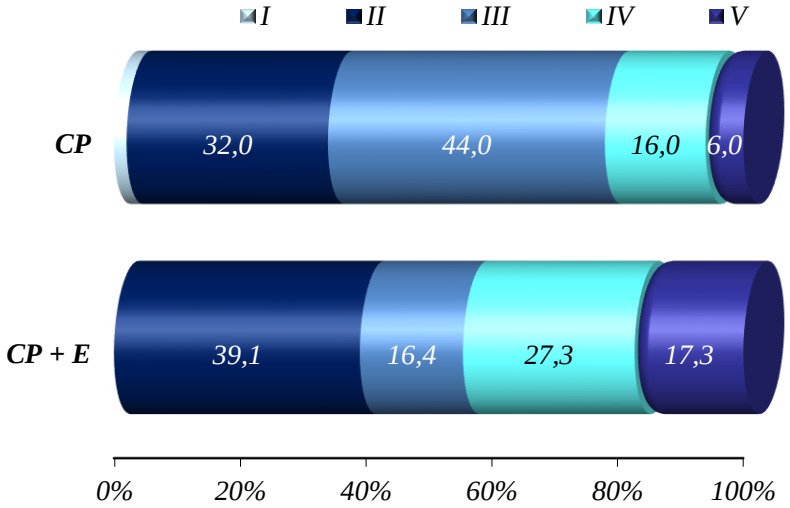

Figure 1. Distribution of patients in groups according to GMFCS levels

The prevalence of epilepsy among CP patients was quite low and amounted to 8.11% ± 2.15%. The mean age of seizures onset was 20.4 ± 27.2 months: 16.9 ± 3.24 months in patients with the quadriplegia , 20 ± 4.8 months in the hemiplegia, 37.3 ± 9.7 months in the diplegia , 19 ± 19.7 months with ataxic and 6 ± 6.2 months with hyperkinetic CP. The mean age of generalized tonic-clonic seizures onset was 26.3 ± 31.2 months, focal seizures 22.1 ± 28 months, and absences 24.6 ± 31.5 months. We found that in patients with myoclonus (3.8 ± 1.9 months) and tonic (infantile) spasms (9.3 ± 15.7 months) attacks began much earlier , usually during the first year of life ($P < 0.05$).

Status epilepticus was observed in 8 children with epilepsy (7.3%), most of whom were children with quadriplegic CP (37.5%).

The following types of seizures were recorded in children with epilepsy (p=0.02): tonic-clonic generalized in 27 (24.6%), partial complex/simple in 59 (53.6%), tonic (infantile) spasms in 15 (13, 6%), 5 (4.6%) patients had myoclonic seizures, 3 (2.7%) had absences, and 1 (0.9%) patient had mixed types of seizures. The most frequent epileptic seizures occurred in the spastic quadriplegic CP in 84 (52.5%) patients, followed by spastic hemiplegic CP in 40 (25%), spastic diplegic

CP in 19 (11.9%). Less commonly, seizures were detected in ataxic and hyperkinetic CP patients in 10 (6.2%) and 7 (4.4%), respectively.

The study identified possible risk factors for the development of epilepsy in children with CP by comparing various indicators in patients in the main and control groups. Hypoxic-ischemic brain injury was one of the most common pathologies in children in both groups, to varying degrees. It was observed in 97 (88.2%) CP children with epilepsy and in 48 (96%) without epilepsy.

In the main group, 84 (76.4%) children were born naturally, and 26 (23.6%) by caesarean section. In the control group, 33 (66%) - naturally, 11 (22%) - by caesarean section. In the group of patients with epilepsy, 69 (62.7%) were full-term and 41 (37.3%) premature babies. In the non-epilepsy group, 28 (56%) were term infants, while 22 (44%) were born prematurely. Birth weight was also analyzed in patients. In 75 (68.2%) children with CP and epilepsy, birth weight was >2500 g, and in 35 (31.8%) children <2500 g. In the group of only CP children, birth weight was distributed as follows: y 33 (66%) patients >2500 gr., and in 17 (34%) <2500 gr. However, it cannot be considered statistically significant as a risk factor for the development of subsequent epilepsy ($p = 0.785$).

All children had their head circumference measured upon admission to the hospital. Microcrania was recorded in 16 (14.5%) children in the main group and in 6 (12%) children in the control group. In general, head sizes in children with and without epilepsy were similar. Differences between groups were not statistically significant ($P > 0.05$) in rates of preterm birth, low birth weight, and multiple pregnancy.

The presence of infection during pregnancy in the mother occurred both in the main (40%) and control (22%) groups. Most of them were intrauterine infections (TORCH-infections) needs to be marked. Statistical analysis showed that maternal infectious diseases during pregnancy increased the risk of epilepsy in patients with CP by more than 2.5 times (OR = 2.6, 95% CI 1.2–5.6, $p = 0.027$).

It should be noted that 24 (21.8%) parents of patients with CP and epilepsy and 8 (16%) parents of patients with CP had a consanguineous marriage (cousins and second cousins). In addition, in

the main group, 9 (8.2%) children had a family history of epilepsy (OR=8.08, p=0.038).

A history of typical febrile seizures occurred in 25 (22.7%) patients in group 1 and in 5 (10%) patients in group 2 , further 36.6% of them developed partial (simple/complex), and 30% generalized epileptic seizures.

Neonatal seizures were registered in 25 (22.7%) children in the main group and 3 (6%) children in the control group. There was a statistically significant difference between groups in this parameters ($p<0.05$). Moreover, in the epilepsy group with a history of neonatal seizures, in the future, partial (35.7%) and generalized tonic-clonic (25%) seizures were most common. Factor analysis revealed that neonatal seizures increase the risk of epilepsy (OR = 4.4, 95% CI 1.2–15.3, p = 0.010). Based on the foregoing, active surveillance is recommended for all children with neonatal seizures in order to promptly identify epilepsy and other anomalies of the nervous system for appropriate treatment.

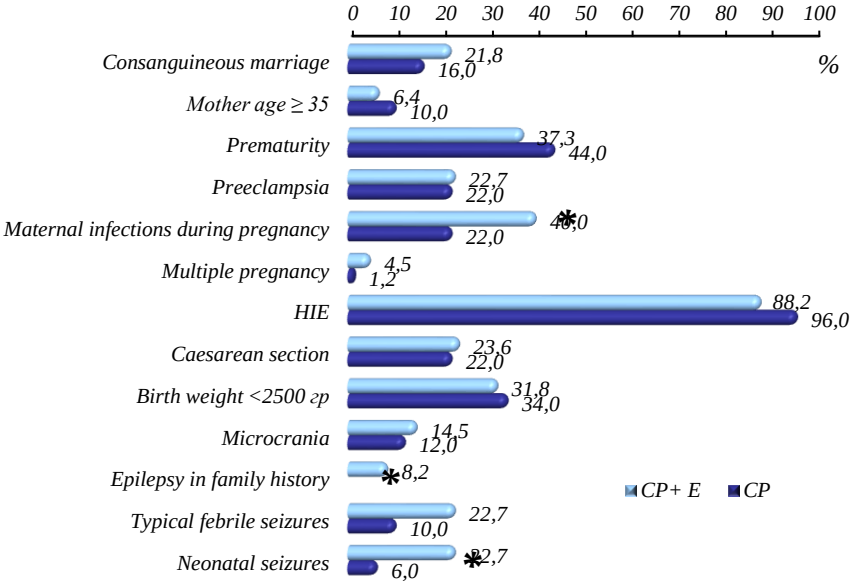

Figure 2. Risk factors in the studied groups

Although it is known that perinatal and postnatal factors increase the risk of developing epilepsy in CP, we could not find an association between them (OR <1), with the exception of neonatal seizures (OR = 4.4), as well as past infectious diseases in the mother during pregnancy (OR =2.6) and the risk of developing epilepsy.

In our study, we also tried to study the available data on comorbid conditions in CP patients , in particular anemia , hearing and vision impairment , and mental retardation. Among our patients , hearing impairment was observed in 5 (3.1%) of them , mainly sensorineural hearing loss type. Vision problems occurred in 8 (5%) patients. However, there was no statistically significant difference in these parameters between patients with or without epilepsy.

As for the cognitive and mental development of patients with CP, only in 23.1% of children it corresponded to age. When comparing CP patients with and without epilepsy, we did not find a significant difference in this indicator ($p>0.05$). Considering cognitive development of patients by different types of CP, it is interesting to note that the most severe cognitive impairment was detected in the quadriplegic CP (75%). In children with hemiplegic CP, more often than others (46.8%) mental and cognitive development corresponded to age.

In the EEG in 60 (54.5%) patients in the group with epilepsy epileptiform activity was recorded and among them ,the focal epileptiform activity was most commonly recorded in 35 (31.8%)cases .Focal epileptic activity presented in our patients included the following patterns: sharp-slow wave complexes (often accompanied by regional deceleration), slow waves, and polymorphic epileptic activity (combination of sharp waves, spikes, peak-wave complexes). Moreover, the patterns were more often observed in the central regions. In patients with such changes both simple with the preservation of consciousness and local convulsions, and complex ones with loss of consciousness focal seizures were mainly detected.

In the control group without epilepsy, the EEG mainly showed changes in background activity (48%). Statistical analysis of the data revealed that the presence of generalized (OR = 28.62, p = 0.02) and mostly focal (OR = 47.49 p = 0.007) epileptiform activity on the EEG may be risk factor for epilepsy in children with CP. As for the area of

electroencephalographic changes on the EEG, it should be noted that they were more often observed in the fronto-central (11.8%) and centro-parietal regions (10.9%). EEG changes during hyperventilation/photostimulation were noted only in 4 (3.6%) CP patients with epilepsy.

Epileptiform activity was more frequently registered in spastic quadriplegia (60%), which may be associated with more severe brain damage. It is interesting to note the impact of epileptiform activity on the speech of CP patients. Among our patients with cerebral palsy, speech problems were detected in 79.6% of children. Speech impairment was predominantly observed in patients with epileptiform activity (focal and generalized) on the EEG (36.5%). In addition , changes in the presence of focal epileptiform activity mainly were seen on the fronto-central (15.4%) and centro-parietal (23.1%) brain regions.

CT/MRI studies of the brain were performed in all 160 CP patients. Assessing the overall picture of changes, it can be noted that the normal results of CT/MRI studies were obtained in 21 (13.12%) patients. The most frequently detected changes included predominant white matter injuries (38.13%), in particular, periventricular leukomalacia and miscellaneous lesions (25.63%) of the brain.

Table 1.

EEG changes in CP patients with and without epilepsy

	CP patients with epilepsy n=110 (%)	CP patients without epilepsy n=50 (%)	P	OR (95% CI)
Normal	4 (3,64%)	18 (36%)	0	
Generalized slow waves	10 (9,1%)	5 (10,0%)	0,855	
Focal slow waves	18 (16,4%)	3 (6,0%)	0,084	
Generalized epileptiform activity	24 (21,8%)	0 (0%)	0,020	28,61 (1,7-481)
Focal epileptiform activity	35 (31,8%)	0 (0%)	0,007	47,49 (2,8-792)
Multifocal epileptiform activity	1 (0,9%)	0 (0%)	0,843	
Hypsarrhythmia	3 (2,72%)	0 (0%)	0,434	
Changes associated with HV /photostimulation	4 (3,64%)	0 (0%)	0,334	
Abnormal background activity	11 (10%)	24 (48,0%)	0	

During neuroimaging in 99 (90.0%) CP patients with epilepsy and in 40 (80%) CP patients without epilepsy abnormalities were detected and this changes differed between groups. In the group of CP patients with epilepsy, changes predominately in gray matter were detected more often (20.9%) compared with CP patients without epilepsy (10%) (p=0.092). The frequency of predominant white matter injuries in our patients in the groups (p=0.91) did not differ (40.9 and 40%; p=0.91). Changes in CP with epilepsy included predominant white matter injuries in 43 (39.1%), predominant gray matter injuries in 23 (20.9%), miscellaneous lesions in 27 (24.5%), brain malformations in 5 (4,5%) patients. In 11 (10%) children, the scans were without abnormalities. In both groups, predominant white matter injuries of the brain was most often observed. In our patients, this pathology was presented as periventricular leukomalacia (PVL). When comparing the two groups, predominant damage to the gray matter of the brain was more often detected with a combination of CP and epilepsy.

In CP without epilepsy, the following brain abnormalities were detected: predominant white matter injuries in 18 (36%) , predominant gray matter injuries in 6 (12%) , miscellaneous lesions in 13 (26%) , brain malformations in 3 (6%) patients. In 10 (20%) patients no changes were found.

When analyzing the data of our study, no correlation was found between the results of EEG and MRI/CT.

All 110 patients were taking antiepileptic drugs (AEDs) during this study. The main used anticonvulsants were sodium valproate (73.6%) and carbamazepine (40.9%). Vigabatrin (44.4%) and clobazam (66.7%) were more commonly administrated for infantile spasms in combination with other AEDs, while topiramate was mainly used for generalized seizures (50%). Fifty-five (50%) patients had well-controlled epilepsy with monotherapy, with valproate being the most commonly used in 47.6% cases. Polytherapy (two AEDs or more) was used in 55 (50%) patients of the main group. This observation may be partly due to the fact that in our study there was a higher proportion of patients with quadriplegia and drug-resistant epilepsy, so the management of epileptic seizures in such patients was

difficult. 39(35.5%) patients received two anticonvulsants for seizures management. Three drugs were used in 16(14.5%) children mainly generalized tonic-clonic and focal seizures, as well as infantile spasms. Monotherapy was widely used in spastic quadriplegia in 29 (52.7%) patients, in nine patients with spastic diplegia (12.5%) and hemiplegia (12.5%), in five patients with ataxic CP (9.1%). Polytherapy mostly used in quadriplegic CP patients , i.e. in 11 patients (68.8%). In spastic hemiplegic CP (16.4%) and diplegic CP (16.4%) , polytherapy was used in two cases, in ataxic CP in one case (6.2%) .

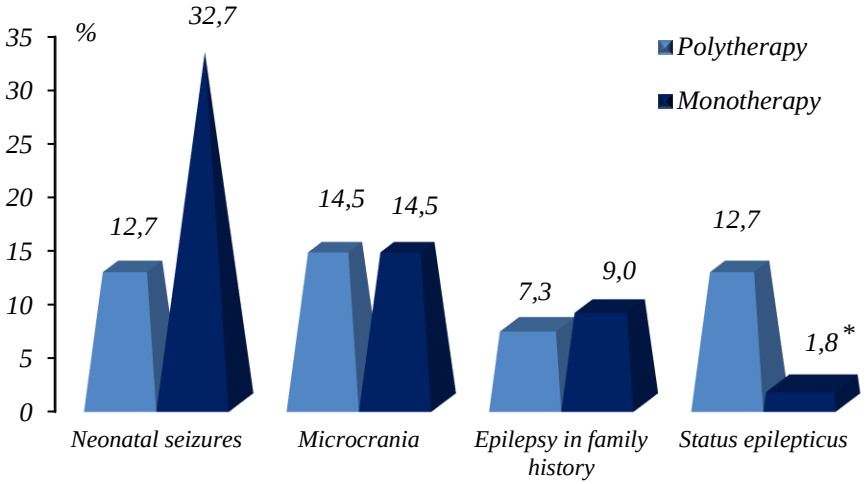

Figure 3. Clinical characteristics in the use of mono- and polytherapy in CP patients.

Possible risk factors for polytherapy (2 or more AEDs) in patients with CP and epilepsy were analyzed. Factor analysis was used to evaluate such indicators as the presence of neonatal seizures, microcephaly, a positive family history of epilepsy, the type of seizures, the CP type , EEG and neuroimaging changes , as well as the level of motor impairment according to GMFSC. History of status epilepticus in patients during the course of the disease (OR=3.34 ; p=0.015) in our study was identified as a predictor of polytherapy in CP patients with

epilepsy. At the same time, the analysis of other variables did not reveal statistically significant data (p>0.05). The prevalence of seizures and the severity of motor impairment in patients were analyzed. Less commonly, epileptic seizures occur in children with mild motor impairments (GMFCS level II 44.9%). In patients with very frequent seizures and poor seizure control, the GMFCS level V was observed more often (30.8%).

Despite treatment with various anticonvulsants, epileptic seizures occurred very frequently (several times a week/day) in 26 (23.6%) CP patients. The majority of cases were tonic (infantile) spasms (38.5%). Drug-resistant epilepsy was more common in children with spastic quadriplegia (57.7%). None of the children with tonic (infantile) spasms reached a period without seizures for more than 1 year. In 15 CP children (13.6%) with epilepsy, seizures remission was achieved for a period of 6 months.

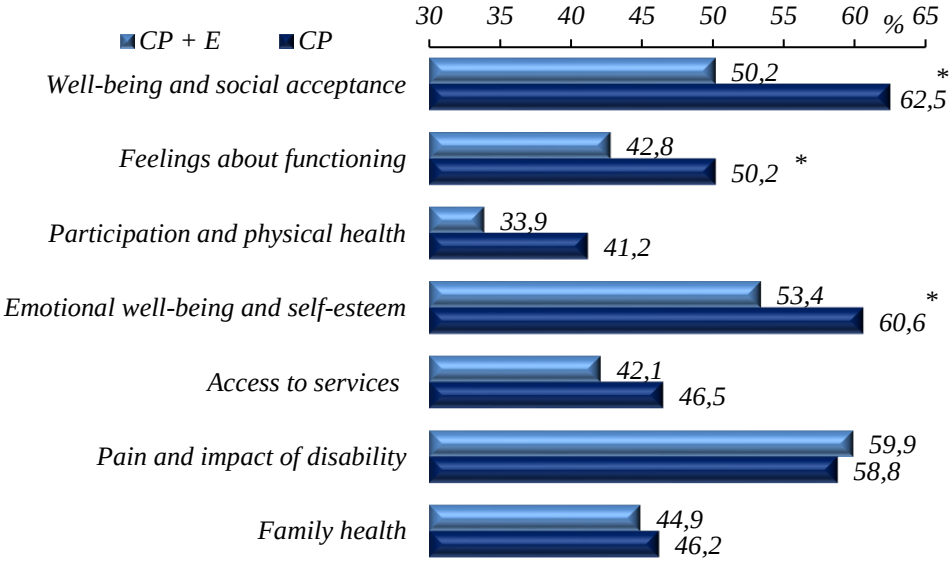

Figure 4. Patients quality of life according to the CP QOL-Child questionnaire.

In the course of this study, we tried to analyze the impact of epilepsy on the quality of life of children with cerebral palsy those on treatment at the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku and the Neurological Department of the Teaching and Therapeutic Clinic of the AMU in Baku. We conducted a survey of 79 CP patients aged 4 to 12 years , of which 54 patients was with epilepsy and 25 of them had no history of epileptic seizures. There were no significant differences between the groups in terms of age and sex in children ($p > 0.05$). The majority of patients in both groups were boys, 64.8% and 80%, respectively. The predominant form of cerebral palsy in children with epilepsy was quadriplegic (46.3%), while in children without epilepsy it was hemiplegic (48%). To assess the quality of life, we chose a modern specific questionnaire for the study of quality in CP patients (CPQOL - Child), which was not previously used in our patients. Significant differences were found in the quality of life of CP patients with and without epilepsy. Thus, when a patient has cerebral palsy and epilepsy, a significant decrease in the "Social well-being and acceptance", 50.2 and 60.7, respectively ($p = 0.0$), characterizing the general social adaptation of the child, is noted to a greater extent.

A decrease was found in the presence of epilepsy in "Feelings about functioning" 42.8 in the main group and 50.2 in the control group ($p = 0.019$), indicating a significant limitation of social contacts, a decrease in the level of communication due to a deterioration in physical condition.

In addition, in the presence of epileptic seizures, the "Emotional well-being and self-esteem " decreases - 53.4 in patients of the main and 60.6 control groups ($p = 0.007$), respectively, which indicates the patient's fatigue, feeling of being exhausted.

We also studied the change in quality of life aspects in CP children regarding various types of epileptic seizures. The lowest indicators of "Participation and physical health" in CP children and epilepsy were observed with focal seizures (32.98) and tonic (infantile spasms) (32.83). "Emotional well-being and self-esteem" more often suffered with absences (52.77). The "Well-being and social acceptance" was the lowest in children with generalized tonic-clonic seizures (49.85).

Violation of "Feelings about functioning" was observed to a greater extent in the presence of generalized tonic-clonic seizures (41.93) and absences (41.72).

An analysis of motor impairment was carried out according to the GMFCS system for assessing motor functions and compared with different aspects of patients QOL . The level of GMFCS has a strong correlation with physical independence, mobility, clinical course, and aspects of social integration. The level of motor function impairment on the GMFC scale was determined by the physician from I to V, where V is the most serious motor function impairment during daily activities. Most often among patients of both the main and control groups, the GMFCS level II was observed (59.3% and 60%). However, in CP patients with epilepsy more severe motor impairments was noted more often than in the control group. Thus, in children with epilepsy, GMFCS level IV was detected in 14.8%, and GMFCS level V in 13%, among CP children without epilepsy, GMFCS level IV and GMFCS level V were registered in 4% of patients.

It is worth mentioning that our patients with cerebral palsy and epilepsy who used 2 or more AED´s (polytherapy) for the management of epileptic seizures showed a decrease in the quality of life in the "Social well-being and acceptance", "Feelings about functioning" and "Participation and physical health" compared with those who used 1 AED (monotherapy).

In the course of a retrospective study, the medical records of CP children diagnosed epilepsy from the Children's Neurology Hospital of the public legal entity Scientific-Research Pediatric Institute named after K. Farajova in Baku for 2013-2017 were analyzed. For the entire period, 13112 children with a diagnosis of cerebral palsy admired to the neurological hospital, of which 2137 children the diagnosis of cerebral palsy was made for the first time, among them 62% were boys (1356) and 38% (781) were girls. Epilepsy were detected in 90 CP children. According to medical records, 32 (35.6%) mothers had an infectious disease during pregnancy, 44 (48.9%) babies were born prematurely, 24 (26.7%) babies were born weighing less than 2500, 5 (5,6%) children were born in multiple pregnancies. Hypoxic-ischemic brain injury was one of the most common pathologies in children with

epilepsy and cerebral palsy (97.7%). It should be noted that 32 (35.6%) of the patients' parents had a consanguineous marriage. In these patients, the possible influence of a genetic factor on the development of the disease is not excluded. Typical febrile seizures occurred in 17 (19%) patients history. Neonatal seizures were observed in 12 (13%) children ($P<0.01$). Further in 2 of them were observed generalized tonic-clonic seizures, 8 children had focal seizures, and 2 patients had tonic spasms . In CP children and epilepsy with a history of neonatal seizures mostly focal seizures (67%), generalized tonic-clonic and tonic spasms (33%) later on occurred.

Regarding the CP type in patients 50 (55.6%) of them had spastic quadriplegia, 16 (17.8%) spastic hemiplegia, 11 (12.2%) spastic diplegia, 11 (12.2%) ataxic CP, 1 (1.1%) hyperkinetic CP and 1 (1.1%) mixed CP. Seizure types were distributed as follows: tonic-clonic generalized seizures in 35 (38.9%), simple/complex focal seizures in 49 (54.4%), tonic spasms in 5 (5.6%), and myoclonic seizures in 1 (1 .1%) patient. The prevalence of epilepsy among CP patients according to medical records was 4.21% ± 0.43%.

The mean age of seizure onset was 17 ± 21 months: 16.8 ± 3.1 months in spastic quadriplegia , 21.6 ± 6.09 months in spastic hemiplegia, 16.7 ± 5.05 months in spastic diplegia .In majority of children (51 /56.7%); the first seizure occurred before 9 months in 58 (64.4%) children under one year and in 42 (35.6%) children after 1 year. Patients with myoclonic seizures and tonic spasms were found to have seizure onset much earlier, usually within the first year of life ($P < 0.05$, retrospectively).Epileptic seizures mainly occurred in spastic quadriplegia in 50 (55.6%) CP patients, followed by spastic hemiplegia in 16 (17.8%) patients. Most of the children in the study had mental retardation. Only 27 (30%) children developed according to their age. Mental retardation mostly was observed in the quadriplegic type of cerebral palsy (55.6%). In CP patients in combination with epilepsy, various changes were detected during neurological examination. Common changes in the neurological status included dysarthria (35.6%), central paresis of the facial nerve (33.3%), strabismus (37.8%), mostly convergent (76.4%), nystagmus (13.3%) and swallowing difficulties (4.4%).

In the majority of cases EEG revealed epileptiform activity (50%), it was more often detected in spastic quadriplegia (57.7%).

Changes during neuroimaging occurred in 45 (86.5%) patients with a predominance of brain white matter injuries (28.8%).

Our research made it possible to study the prevalence, features (onset time, frequency and nature of seizures) and the course of epilepsy, as well as to evaluate the quality of life in patients with cerebral palsy.

CONCLUSIONS

1. Retrospective analysis of medical materials for 2013-2017 showed the predominance of the quadriplegic type (55.6%) of cerebral palsy among patients and focal simple / complex (55%) epileptic seizures. The mean age of seizures onset was 17 months [1,2,4].
2. The prevalence of epilepsy in CP children (8.11% ± 2.15%) varies depending on the type of cerebral palsy. In majority of cases epileptic seizures (55.5%) occurred in the spastic quadriplegia. Most of the seizures among our patients were focal and secondarily generalized with a debut of up to 2 years. In addition, children with cerebral palsy and epilepsy have more severe motor impairment according to the GMFCS scale [3, 9,14].
3. Positive family history for epilepsy (OR=8.08, p=0.038), neonatal seizures (OR=4.4, p=0.010), maternal infectious diseases during pregnancy (OR=2.6, p= 0.027), as well as the presence of generalized (OR = 28.62, p = 0.02) and focal (OR = 47.49 p = 0.007) epileptiform activity on the EEG were identified as risk factors for the development of epilepsy in patients with cerebral palsy. [5,11,14].
4. The use of modern neurophysiological methods helps in the correct diagnosis and choice of management tactics for patients with cerebral palsy. In combination of CP and epilepsy EEG demonstrate mainly focal (31.8%, p=0.007) and generalized (31.8%, p=0.02) epileptiform activity [7,8,13,14].

5. The quality of life of patients with cerebral palsy significantly decreases in the presence of epilepsy. In our study, the significant difference was observed in "Emotional well-being and self-esteem" (p=0.007), "Social well-being and acceptance" (p=0.0), and "Feelings about functioning" (p=0.019) [6,10,14].
6. When cerebral palsy is combined with epilepsy, antiepileptic polytherapy (50%) is often used for clinical management of children. Status epilepticus in CP patients during the course of the disease increases the risk of using several antiepileptic drugs (OR = 7.74, p = 0.028), although complete control over seizures is not always achieved [12,14].

PRACTICAL RECOMMENDATIONS

1. All children diagnosed with cerebral palsy, especially those who are at high risk, should be carefully examined for the occurrence of epilepsy in order to start early intervention, which can be crucial in the lives of these patients.
2. EEG is an essential method for diagnosing epilepsy, which makes it possible to identify specific epileptiform changes in patients with cerebral palsy. In difficult cases, EEG monitoring is recommended to detect epileptic activity and determine the type of seizures.
3. The use of specific modern questionnaires to determine the quality of life of children with cerebral palsy is an important tool for choosing the right tactics for managing these patients.
4. Prediction of drug-resistant epilepsy in patients with cerebral palsy is a crucial task, since the rapid identification of patients at high risk of developing epilepsy will allow doctors to prescribe them early management with antiepileptic drugs, as well as other surgical methods of treatment.

LIST OF PUBLISHED SCIENTIFIC WORKS ON THE SUBJECT OF DISSERTATION

1. Тагиева М.Р, Магалов Ш.И., Мамедбейли А.К.Эпилепсия и детский церебральный паралич//Азербайджанский Психиатрический Журнал; № 1 (33)-2019, стр.104-117
2. Тагиева М.Р , Магалов Ш.И., Мамедбейли А.К. Характеристика пациентов с эпилепсией и различными формами детского церебрального паралича // Национальный Научно-практический журнал Неврологии; № 2 (16) 2019; стр.48-54
3. Тагиева М.Р , Магалов Ш.И., Мамедбейли А.К. Эпилепсия при детском церебральном параличе// Национальный Научно-практический журнал Неврологии; №1 (15)2019 , стр.26- 35
4. Taghiyeva M.R Cerebral palsy and epilepsy // сборник материалов 13 Конгресса Педиатрического Неврологического Общества; 2019, стр.96
5. М.Р.Тагиева Современный подход к диагностике детского церебрального паралича //Глобальная наука и инновация 2020: центральная азия» № 5 (10). август 2020 серия «медицинские науки»; стр.40-43
6. Тагиева М.Р ,Магалов Ш.И., Мамедбейли Влияние эпилепсии на качество жизни у детей с детским церебральным параличом.//Национальный Научно-практический журнал Неврологии №2 (16) 2019, стр.106
7. М.Р.Тагиева Ранняя диагностика Детского Церебрального Паралича// Международный неврологический журнал; №8 (110) 2019, стр.
8. Влияние нарушений двигательных функций на проявления эпилепсии у детей с ДЦП “Ш.И., Магалов, А. К.Мамедбейли, М.Р.Тагиева. Сагламлыг-2020 №5;108-115
9. Тагиева М.Р Эпилепсия при детском церебральном Параличе и качество жизни // ТиббвяЕлм Журналы, №1 (19) 2020, стр. 53-58

10. Тагиева М.Р,Мамедбейли А.К. Использование нейрофизиологических и радиологических методов для выявления основных предикторов развития эпилепсии у детей с церебральным параличом // Медицинские Новости№5· 2021 ; стр.73-75
11. Тагиева М.Р,Мамедбейли А.К. Факторы риска развития эпилепсии у детей с детским церебральным параличом //Казанский медицинский журнал. ; №4 Т. 102, 2021, стр. 421-427. Doi: 10.17816/KMJ2021-421
12. Тагиева М.Р.Эпилепсия у детей с церебральным параличом и особенности медикаментозной терапии//ТиббвяЕлм Журналы, №1 (19) 2020, стр.53-58
13. Taghiyeva M.R Early diagnosis in Cerebral Palsy, Taghiyeva M.R//Азербайджанский Журнал Перинатологии и Педиатрии ;№2, T.5, 2019, s.90-91
14. Тагиева М.Р,Мамедбейли А.К. Особенности эпилепсии при церебральном параличе// сборник материалов конференции, посвященной актуальным проблемам медицины;2021,стр.261.
15. Taghiyeva M.R.,Mammadbayli A.K.Epilepsy features in cerebral palsy patients.// сборник материалов 14 Конгресса Педиатрического Неврологического Общества; 2022, стр.224

List of conditional abbreviations

CP – cerebral palsy
EEG - electroencephalography
CT - computerized tomography
MRI - magnetic resonance imaging
CP QOL-Child- Quality of Life Questionnaire for Children with cerebral palsy
ICD-10 – International Statistical Classification of Diseases
GMFCS- Gross Motor Function Classification System
TORCH- Toxoplasmosis ,Rubella, Cytomegalovirus, Herpes simplex virus
HIE- Hypoxic Ischemic Encephalopathy
AED- Anti Epileptic Drug
PVL – Periventricular Leukomalacia

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