Epilepsy in cerebral palsy. Comprehensive questionnaire research performed in three different provinces in Poland

Padaczka w mózgowym porażeniu dziecięcym. Badania populacyjne na podstawie wyników z trzech województw

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ABSTRACT

Introduction: Children with cerebral palsy (CP) often suffer from associated neurological problems and the association between CP and epilepsy is considered to be an important issue. In last years advantages in epilepsy treatment have been made (several new antiepileptic drugs have been introduced). Aim of study: Determination of the prevalence of CP among children with epilepsy in the group of patients embraced by the care of developmental neurology out-patient clinic in three provinces in Poland as well as determination of major types of antiepileptic treatment. Materials and Methods: The study group consisted of 1115 consecutive patients presented in outpatients’ child-neurology clinics in three province-cities in Poland (Gdansk, Lodz and Kielce). We isolated the group of patients with CP and analysed their type of epilepsy and type of received treatment as well as overall response rate for treatment comparing those results with non-CP epilepsy group. Results: Among 1115 patients with epilepsy – 178 had CP (16%). Children with CP had mostly secondarily generalized seizures (62%), tonic seizures (22%), complex partial seizures (20%), myoclonic seizures (10%), atypical absence seizures (8%). Majority of CP children were treated with valproic acid (74%), than carbamazepine (41%). Interestingly statistically significant more children with CP than with “pure” epilepsy were treated with benzodiazepines. The success rate (more than 75% of seizure reduction) was 54.6% (89% on monotherapy), this was significantly less that in isolated epilepsy group. Conclusions: Epilepsy is a serious co-morbidity in children with CP. There are several factors which need to be considered when starting treatment, especially that the effectiveness of AEDs treatment seems to be less effective in children with CP.

Key words: epilepsy, cerebral palsy, antiepileptic treatment, children

STRESZCZENIE

Wprowadzenie. Współwystępowanie mózgowego porażenia dziecięcego (MPD) i padaczki jest częstym zjawiskiem i wymaga szczególnej uwagi ze strony neurologów dziecięcych. W ostatnich latach dokonał się znaczny postęp w leczeniu padaczki oraz zwiększła się znacznie liczba dostępnych na rynku leków przeciwpadaczkowych, co pozwoliło na dobór optymalnej metody leczenia u pacjentów z MPD. Cel pracy. Określenie częstości występowania padaczki oraz sposobu jej leczenia u pacjentów z MPD w trzech regionach Polski. Material i metody. Badaniem objęto 1115 dzieci z rozpoznana padaczką oraz współistniejącym MPD pozostających pod opieką trzech poradni neurologicznych dla dzieci (w Gdańsku, Łodzi i Kielcach). Rodzaj padaczki, a także metody i skuteczność jej leczenia zostały poddane analizie. Grupę kontrolną stanowiły dzieci z izolowaną padaczką. Wyniki. Padaczka występowała u 178 (16%) pacjentów z MPD. Dzieci z MPD miały najczęściej złożone wtórnie uogólnione (62%), ponadto występowano napady toniczne (22%), częściowe złożone (20%), miokloniczne (10%), atypowe napady nieświadomości (8%). Większość dzieci z MPD była leczona kwasem walproinowym (74%) i karbamazepiną (41%). Benzodiazepyny stosowano statystycznie częściej u dzieci z padaczką niż u dzieci z MPD. W tej grupie przeważyły napady częściowe złożone wtórnie (62%), nadal występowano napady toniczne (22%), częściowe złożone (20%), miokloniczne (10%), atypowe napady nieświadomości (8%). Większość dzieci z MPD była leczona kwasem walproinowym (74%) i karbamazepiną (41%). Benzodiazepyny stosowano statystycznie częściej u dzieci z padaczką i współistniejącym MPD niż w grupie z izolowaną padaczką. Sukces terapeutyczny (zmniejszenie liczby napadów o co najmniej 75%) osiągnięto u 54,6% pacjentów (z tego u 89% stosowano monoterapię) – odsetek ten był znacząco niższy niż w grupie dzieci z izolowaną padaczką. Wnioski. Padaczka często występuje u dzieci z MPD. Skuteczność leczenia przeciwpadaczkowego w tej grupie jest niższa niż w grupie dzieci z izolowaną padaczką.

Słowa kluczowe: padaczka, porażenie mózgowe, leczenie padaczki, dzieci
Cerebral palsy (CP) is a non-progressive disorder, caused by permanent brain damage at early stage of development. Patients with CP present a variety of symptoms and abnormalities, that creates all together characteristic neurological syndromes of heterogeneous etiology. Movement disorders are often accompanied by decrease in cognitive functions, sight or hearing impairment and speech delay. Clinical picture is frequently associated with presence of epilepsy. According to the world-wide literature, epilepsy exists in about 15 to 60 [1] or even 90% [2] patients with diagnosed CP. That patient constitutes about 0.5–1% of general population. The frequency of epilepsy varies among different types of CP – higher in spastic quadriplegia and the lowest in spastic diplegia and dystonic CP [3, 4]. According to Gururaj [1], CP epilepsy constitutes about 10–20% of all epilepsies. However, there is still not enough epidemiological data to confirm that percentage.

Correct diagnosis confirming coexistence of both neurological conditions in children is particularly valuable, as ipso facto provides a possibility of prompt pharmacological or neurosurgical treatment implementation. It is highly significant in patients, who not only suffer from physical and mental impairment connected with the presence of CP, but also are at risk of escalated course of epilepsy. Moreover, the age of seizure onset is considerably lower in comparison to children with isolated epilepsy, as well as the monotherapy is commonly found to be ineffective [5].

The aim of this study was to verify the prevalence of CP among children with epilepsy in the group of patients embraced by the care of developmental neurology out-patient clinic in three provinces in Poland as well as determine major types of antiepileptic treatment.

Majority of the scientific research are conducted on numerically low groups of patients and they do not define unequivocally the incidence, the course and prognosis of epilepsy in children with CP. There are also not enough data determining appropriate treating procedures in these patients.

For this reason, the following study was performed to characterize the population of children with concurrent CP and epilepsy with a regard to applied treatment (group 1). Control group consisted of children with isolated epilepsy (group 2). A special attention was paid to seizure onset, neonatal seizures, frequency of particular seizures types, methods of treatment, as well as presence of mental retardation.

We believe that our analysis, conducted on the numerically large group of patients, represents reliable characteristics of CP children with coexisting epilepsy and also constitutes an objective review of actually applied methods of treatment in Poland. We believe that this study will contribute to standardization of antiepileptic therapy in the nearest future and will allow to obtain credible epidemiological data that will enable early diagnosis of epilepsy in children with CP.

**MATERIAL AND METHODS**

There were totally 1115 cases included in the study. All of the patients were attending to the outpatients’ developmental neurology clinics in one of the 3 clinical sites: in Gdaňsk, Lódź or Kielce. Every patient suffered from epilepsy and visited pediatric neurologist from 1st January to 31st December 2005. Among the group of epileptic patients we identified the study group (group 1) and the control group (group 2). The study group consisted of 178 patients with concurrent CP and epilepsy. The control group comprised of 937 children suffering from epilepsy without any other neurological deficits. The age of patients ranged from 9 months to 18 years. The data were collected on the basis of questionnaires, completed by patients, parents or legal representatives and pediatric neurologists during the control visits from January to December 2005. The queries in the questionnaires referred to family history, main diseases, results of neurological examination, methods and outcome of applied antiepileptic treatment. Selected details, that were statistically analyzed, referred to age, gender, neonatal convulsions, seizure onset, type of epileptic seizures, antiepileptic therapy, outcome of applied treatment, classification of the CP, mental retardation.

Obtained results were statistically analyzed and compared. Then, the principal differences between group 1 and group 2 were isolated. A special attention was paid to seizure type, seizure onset, methods and effects of applied treatment.

Definition of neonatal convulsions describes the convulsions during the first 30 days of life.

Types of epileptic seizures were defined according to the International League Against Epilepsy revised classification from 1989 year. Epileptic seizures in patients with CP can take many forms. Due to the fact that they may be difficult to distinguish from involuntary or stereotypic movements, breath-holding spells, swallowing abnormalities, vasovagal syncope and other non-epileptic paroxysmal disorders coexisting with CP [20]. Epileptic seizure was recognized only in conditions that were unambiguous and did not arouse a suspicion of non-epileptic nature.

Good seizure control was defined by 75% or more reduction in number of seizures in a period of 3 months. Seizure-free period of 3 months was another parameter measured in both groups of patients.

Classification of CP included: spastic quadriplegia (spasticity involving all four limbs with involvement of the arms being more marked than or equal to that of the legs), spastic diplegia (spasticity of the lower extremities with a variable but lesser involvement of the upper limbs), spastic hemiplegia (spasticity of the arm and leg on one side), extrapyramidal, ataxic and mixed type (including spastic and extrapyramidal manifestations) [6, 7].

Presence of mental retardation was stated on the basis of psychological or pedagogical diagnosis.

The objectives of the study were explained to the parents or legal representatives of children when possible and also an informed consent was obtained. Statistical analysis using Chi-square analysis, student t-test and Mann-Whitney test was performed. The level p<0.05 was considered as the cut-off value for significance.

**RESULTS**

A total of the 1115 patients were included in the study. There were 178 (16%) children with CP and concurrent epilepsy (group 1), and 937 (84%) children with isolated epilepsy (group 2). Gender proportion of girls to boys in the whole studied population was 520:595 (0.87), respectively, in the group 1 it was 81:97 (0.83) and in the group 2 the proportion was 439:498 (0.88). The age of patients in group 1 ranged from 10 months to 17 years (mean: 6.7 years) and in the group 2 ranged from 9 months to 18 years (mean age: 5.4 years).

Occurrence of particular types of CP in the study group is presented in table I.
It was proved that secondarily generalized tonic-clonic seizures were observed more frequent among children with CP in comparison to control group and this difference was statistically significant (110 patients; 62% in the group 1 vs. 237 patients; 25% in the group 2). The type of seizure that was the most rarely observed in the study population referred to the primarily generalized tonic-clonic seizure (2 patients; 1%; p<0.05).

Frequency of particular seizure types in both groups of patients is presented in the table IV.

All of the patients were receiving antiepileptic drugs (AEDs) through the whole period of the study. 682 of all children (61.3%) were treated by means of monotherapy but still polytherapy proved to be necessary in 433 patients (38.9%). It has been investigated that application of antiepileptic monotherapy among children with CP was significantly smaller than in children with isolated epilepsy (36% vs. 66%). On the other hand, polytherapy composed of two AEDs was the most frequent decision in the group of children with CP (40% in group 1 vs. 22% in group 2, p<0.05). 3 AEDs were applied in 28 patients (16%) from group 1 and 56 patients (6%) from the group 2. More than 3 AEDs were administered to 15 (6%) and 56 (6%) patients group 1 and 2, respectively. These relations are presented at the figure 1.

Good seizure control was obtained in 54% of patients with CP and 87% of patients from control group. Seizure-free period of 3 months was observed in 38% of patients from the 1 group and even 78% of the 2 group.
istered in children with CP. These results occurred to be statistically significant (p<0.05). Valproic acid was also applied very often in children with isolated epilepsy (59% in group 2 vs. 74% in group 1), however, it was not statistically relevant. There was no correlation between the usage of other AEDs and CP (table VI).

Table VI. Treatment of epilepsy according to the presence of CP

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>131 (74%)*</td>
<td>534 (59%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>73 (41%)</td>
<td>365 (39%)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>69 (39%)*</td>
<td>37 (4%)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>46 (26%)</td>
<td>196 (21%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>26 (15%)</td>
<td>178 (19%)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>10 (6%)</td>
<td>84 (9%)</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>8 (4%)</td>
<td>25 (3%)</td>
</tr>
</tbody>
</table>

*p<0.05

DISCUSSION

Incidence of epilepsy connected with CP was estimated on 16% among all epilepsies in studied population. Above investigation was performed on large numerically group of 1115 patients and this aspect amplify the reliability of our findings. Especially as the number of patients in other studies rarely exceeds 100 [1, 10].

Moreover, we also proved as the other authors that spastic quadriplegia and spastic diplegia are the most frequent types of CP associated with epilepsy occurrence [1, 3, 4, 10] and this fact undoubtedly depends on an extension of brain damage.

Epilepsy onset strongly correlated with neurological deficits. The age of first seizures in children with CP was significantly lower than in children with isolated epilepsy. In the group I seizure onset was estimated on slightly over the first year of life. Early epilepsy onset up to 12 months in CP is widely confirmed in the literature [10–14]. Seizure onset between the first and the second year of life were also observed by Paucic-Kirincic in 2005 [9] and Singh in 2003 [15].

Some of the studies consider a relationship between the neonatal convulsions and future presence of epilepsy and other neurological deficits [16, 17]. We also observed this association. There was a twice higher percentage of neonatal convulsions in amnestic in the studied group with CP.

In our research, children with CP presented different types of epileptic seizures. Obtainable scientific data do not describe a direct correlation between classification of CP and characteristic type of epileptic seizures. Due to not unified conditions of the studies (different numerical force of the population or time of observation, etc.), the frequency of particular epileptic seizures vary from 12.9% [19] to 50% [9] for secondarily generalized tonic-clonic seizures or from 44% [19] to even 85% [20] for primarily generalized tonic-clonic seizures. Our findings in group 1 indicate that secondarily generalized tonic-clonic seizures were observed the most frequently. On the contrary, primarily generalized tonic-clonic seizures occurred very rarely in comparison with children from group 2. Definitely, the discrepancies referring to the incidence of different epileptic seizures in CP patients need further investigation.

Majority of patients from the study group were treated with 2 AEDs simultaneously and the improvement was present. Over a half of the patients experienced a 75% reduction in a number of seizures and 38% of patients were seizure-free for at least 3 months. However, these proportions were incomparably higher among children with isolated epilepsy. There were over a half more children with 75% reduction in seizures and almost two times more of seizure-free children for at least 3 months. The number of patients on monotherapy was also significantly higher in children with isolated epilepsy. Although the therapy of epilepsy in CP patients included commonly 2 AEDs, the seizure control in this group was insufficient. It is still a matter of discussion if there is a real demand on switching from monotherapy to 2 AEDs in children with CP or the decision on polytherapy is useless due to the extent brain damage and poor outcome. Assuming all above facts, we can say that necessity of polytherapy in children with concurrent CP and epilepsy has still been unconfirmed. Valproic acid was the most frequently applied antiepileptic specimen in both groups. The percentage of valproic acid administration among children with CP was 15% higher and this proportion occurred to be statistically significant. Subsequent AEDs commonly prescribed in the study group was clonazepam. These decisions were the most likely made due to the extensive range of action of both AEDs.

We also proved that that mental retardation accompanies CP and epilepsy particularly often. It occurred to be three times higher than in the control group.

This study clearly indicates that epilepsy in patients with CP is associated with presence of neonatal convulsions. Moreover, these patients present worse seizure control, even though polytherapy was applied. Mental retardation as well as coexistence of physical handicap and epileptic seizures with potential adverse events of applied AEDs are additional factors, that significantly lower quality of life in patients with CP. Entirety of various conditions and aspects of CP complicated by the epilepsy leads to the general conclusion that it is essential to improve methods of treatment as well as accurate and certain diagnosis, including genetic and prenatal factors determining occurrence of CP in children.
REFERENCES


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