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Epilepsy in Children with Cerebral Palsy

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ABSTRACT

Introduction and aim of the study: Epilepsy is one of the most common disorders in children with cerebral palsy. In addition, due to the variety of symptoms and the possibility of co-occurrence with other disorders, it is often difficult to diagnose. This article presents the epidemiology, pathophysiology, seizure classification, diagnosis, and treatment of epilepsy in patients with CP. In addition, the psychosocial aspect of epilepsy is taken into account and the issue of SUDEP, or sudden unexpected death associated with epilepsy, is presented. The purpose of the study is to show an overview of the current state of knowledge about epilepsy in children with CP.

Materials and methods: The paper analyzes studies in databases such as PubMed, Google Scholar, ResearchGate, and other scientific databases. Clinical studies, preclinical studies, and review papers on the incidence of epilepsy in children with cerebral palsy were searched.

Conclusions: Epilepsy in children with CP is a challenging and important clinical problem. Effective diagnosis, appropriate selection of medications, and subsequent monitoring of treatment are important. In addition, to improve the quality of life and functioning of patients, it is worthwhile to educate parents and caregivers, as well as provide psychological care. In the treatment of children with CP and epilepsy, the cooperation of many specialists such as neurologists, physiotherapists, occupational therapists, and psychologists is crucial. Further research is needed not only on pathophysiology but also on new therapeutic solutions, which will contribute to an even more individualized approach to patients with CP and epilepsy.

Keywords: epilepsy, cerebral palsy, seizures

Introduction

Cerebral palsy is the most common cause of physical impairment in children. The incidence ranges from 1.5 to 3 per 1,000 live births, with a higher rate of cases observed in low- and middle-income countries and specific geographic regions. [1]

The features of cerebral palsy are associated with damage to the immature brain, resulting in later primary impairments, including decreased muscle tone, loss of selective motor control, and balance disorders. [2]

Epilepsy is one of the most common serious brain diseases, affecting more than 70 million people worldwide. It is characterized by a persistent predisposition to induce spontaneous epileptic seizures and has numerous neurobiological, cognitive, and psychosocial consequences. [3]

According to the practical definition of epilepsy proposed in 2014 by the International League Against Epilepsy (ILAE), epilepsy is a brain disease that meets one of three diagnostic criteria. The first is the occurrence of at least two unprovoked or reflex epileptic seizures that occur more than 24 hours apart. The second criterion is the occurrence of one unprovoked or reflex epileptic seizure if the risk of another seizure is high, i.e. at least 60%, which is comparable to the risk of recurrence after two unprovoked seizures. The third criterion is the diagnosis of a specific epileptic syndrome.

Epilepsy occurs in 33-39% of children with cerebral palsy. [4]

Epidemiology

Epilepsy is a serious clinical problem in children with cerebral palsy. It usually reveals itself in the first year of life, although it is most often diagnosed in the first 4-5 years of life. Its incidence depends on the type of cerebral palsy. The highest risk of epilepsy is in tetraplegia (50-94%), and it quite often accompanies hemiplegia (33-50%). In contrast, children with diplegia and the atactic type of CP are less likely to suffer from epilepsy (16-27%). [5]

Risk factors for epilepsy in children with cerebral palsy (CP) are diverse and include both prenatal and postnatal factors.

A study conducted at the Cukurova University Faculty of Medicine Hospital child neurology outpatient clinic between 2006 and 2009 found that children with severe forms of CP, such as tetraplegia or mixed forms, have a higher risk of epilepsy, especially when brain damage involves areas controlling movement and cognitive function. Early onset of epileptic seizures is associated with a poorer prognosis and a higher risk of recurrence.

Brain damage, which can occur as a result of perinatal hypoxia, head trauma, or infection, increases the susceptibility to epilepsy. In addition, comorbid conditions, such as intellectual impairment or vision and hearing problems, also promote the development of seizures. Inadequate treatment, both pharmacological and rehabilitative, can worsen the course of epilepsy, as can genetic factors that affect the brain's sensitivity to damage and response to therapy. [6]

Also, a study conducted in northeastern Poland confirms that one of the main risk factors for the development of epilepsy in children with CP is the severity of the form of the disease. A significantly higher incidence of epilepsy was found in children with spastic tetraplegia, where epilepsy affected 65.6% of cases. Based on logistic regression analysis, the study's authors concluded that factors such as low birth weight, seizures in the neonatal period, seizures in the first year of life, family history of epilepsy, and the presence of brain imaging lesions were significant risk factors.

As for prognosis, epilepsy in children with CP has a different prognosis depending on the type of paralysis. In children with spastic diplegia, seizure control was achieved in 83.3% of cases, indicating a relatively good prognosis in this group. In contrast, in children with spastic hemiplegia, 72.7% of children achieved seizure control. In contrast, in children with spastic tetraplegia, seizure control was much more difficult - only about 39.5% of children with this form of CP had successful seizure control, with the remainder requiring intensive multi-drug treatment. [7]

In conclusion, epilepsy in children with cerebral palsy is a major therapeutic challenge, and its course and prognosis are closely related to the severity of the form of CP. For children with milder forms, such as spastic diplegia, the prognosis is relatively favorable, with seizure control achieved in most cases. In contrast, in more severe forms, such as spastic tetraplegia, seizure control can be much more difficult, and these children require intensive multi-drug treatment.

Pathogenesis and mechanisms of epilepsy in children with CP

The pathogenesis of epilepsy in people with cerebral palsy (CP) is complex and results from brain damage during fetal, perinatal, or early childhood life. Depending on the type of CP, the location of the damage, and its extent, epilepsy can take on different clinical forms and have different responses to treatment. In most children with CP, brain abnormalities can be observed on MRI imaging. [8]

Epilepsy in CP is associated with underlying brain damage and can be classified according to the anatomical site of brain damage; namely the cortex, pyramidal tract, extrapyramidal systems, or cerebellum. [9]

The extent of underlying brain damage must also be recognized: white matter damage, gray matter damage, focal vascular injury, and malformations. [10]

In children with cerebral palsy, white matter damage is most common. They mainly cause spastic cerebral palsy, including diplegia (46.4%), hemiplegia (33.2%) and spastic diplegia. (13,2%). [11]

A study involving 256 children with CP caused by ischemia or hemorrhage, 57 (22%) of whom experienced neonatal seizures and 93 (36%) of whom had epileptic seizures in childhood, found that the presence of damage to the cerebral cortex significantly increased the risk of seizures in childhood and was associated with more severe epileptic syndromes, such as West syndrome, focal epilepsy, and Lennox-Gastaut syndrome. In contrast, children with white matter damage experienced seizures less frequently, and if they did, they were more often milder forms, such as febrile convulsions or self-limiting childhood focal epilepsies. This suggests that the mechanisms of epileptogenesis differ depending on the type of damage. [12]

The findings indicate that epilepsy in CP is not a homogeneous phenomenon, but results from a variety of mechanisms of brain damage, which is reflected in a different clinical course and prognosis. Damage to the cerebral cortex is associated with more severe and more difficult-to-treat forms of epilepsy, while damage to the white matter more often leads to milder seizures with a greater tendency to resolve spontaneously. Understanding these relationships is crucial for the diagnosis, prognosis, and selection of appropriate therapeutic strategies in patients with CP and epilepsy.

Classification of epileptic seizures in children with CP

Epilepsy in children with CP has an early onset, a high initial incidence, and the coexistence of multiple epileptic seizure subtypes.

A study by Archan and colleagues (2022) evaluated the different types of epileptic seizures occurring in children with CP, their frequency, and the clinical factors associated with them. Among the children studied, focal seizures occurred in 37% of patients, generalized seizures in 58%, and combined focal and generalized seizures in 5%. The authors emphasize the need for an individualized approach to the classification and treatment of epilepsy in children with CP, taking into account the diversity of seizures and their relationship to primary brain damage.

Accurate seizure classification is crucial for optimizing therapeutic strategies and improving patients' quality of life. [13]

Similar results were obtained by Zafeiriou and colleagues (1999), who in their study also showed a similar distribution of seizures in children with CP. [14]

Also, a study by Pavone and colleagues (2020) provides valuable information on the types of epilepsy present in children with cerebral palsy (CP). The analysis shows that focal seizures were most frequently diagnosed in this group of patients, followed by generalized seizures, West syndrome, neonatal seizures, and epileptic encephalopathy. In the context of different types of CP, some correlations were observed in the distribution of types of epilepsy. In the case of children with spastic tetraplegia, focal epilepsy was most often found, followed by generalized epilepsy and epileptic encephalopathy. In hemiplegia cases, on the other hand, focal epilepsy was predominant and usually involved the side of the body affected by hemiparesis, indicating the location of the epileptic focus in the brain. This study underscores the complexity and diversity of epileptic seizures in children with CP, which is crucial for undertaking appropriate therapeutic strategies. [15]

Diagnosis

The diagnosis of epilepsy is made based on family and personal history, semiology, and features of clinical events. However, the gold standard for diagnosis is the electroencephalogram. [16]

Epileptic seizures can take many forms and present challenges in distinguishing them from other involuntary movements. Indeed, children with CP may experience non-epileptic disorders such as breath-holding spells or vasovagal syncope.

Video recordings can be helpful, especially if movement artifacts prevent proper interpretation of the EEG. It is worth remembering that the EEG of children with CP may show changes comparable to those seen in epilepsy, even if no clinical seizures have occurred. [17]

A study conducted at the Neurodevelopmental Clinic in Tuen Mun Hospital, Hong Kong on neuroimaging in the diagnosis of epilepsy found that computed tomography (CT) brain scans of children with CP showed structural abnormalities in 74% of patients. Among the lesions detected were cerebral atrophy, focal brain infarcts, generalized encephalomalacia, schizencephaly, and hydrocephalus. Structural brain abnormalities detected by imaging studies are a significant risk factor for the development of epilepsy in children with CP. Compared to the control group, in which significant CT lesions were significantly less frequent (10%), these findings suggest that brain damage in CP promotes the occurrence of epileptic seizures. [18]

Also, a study conducted at the Pediatrics Department of the University of Catania, Italy confirms that neuroimaging studies play a key role in the diagnosis of epilepsy in children with cerebral palsy. It showed patients with CP have a variety of structural brain lesions that can predispose to epileptic seizures. Among the most common lesions found in children with CP were encephalomalacia with porencephalic cysts, white matter lesions resulting from hypoxia-ischemia, and brain malformations such as thinning of the corpus callosum, polymicrogyria, and microcephaly. The study showed that children with quadriplegic CP were more likely to have congenital brain malformations, while hemiplegic cases were dominated by sequelae of ischemic infarction resulting from perinatal thrombosis. [15]

The results of a study involving the incidence of epilepsy in children with hemiplegia indicate that epilepsy was more common in children with more extensive brain damage, especially resulting from perinatal stroke and hypoxia-ischemia. EEG studies in children with epilepsy showed asymmetrical discharges of spikes and slow waves, indicating focal epileptiform activity. Magnetic resonance imaging (MRI) showed that epilepsy more often co-occurred with unilateral cerebral infarcts, white matter atrophy, and cortical malformations. Despite the frequent presence of these structural changes, not all children with cerebral palsy develop epilepsy, suggesting that brain damage alone is not the only risk factor. Therefore, a comprehensive diagnosis should include not only neuroimaging studies but also a detailed clinical and EEG analysis to more accurately assess the risk of epileptic seizures. [19]

Treatment of epilepsy in children with CP

According to the 2020 study, pharmacological treatment of epilepsy for cerebral palsy can include the use of monotherapy or polytherapy. First-line drugs include valproic acid, topiramate, phenobarbital, and levetiracetam. Second-line drugs include vigabatrin, lamotrigine, clonazepam, clobazam or gabapentin. Treatment results may depend on the type of epilepsy and the type of seizures a person has. In the same study, of 46 children with epilepsy and cerebral palsy, 21 received polytherapy, 16 received monotherapy, seven received no therapy, and two children did not participate in the follow-up. The use of combined antiepileptic drugs was shown there to be more frequent in the group of children with tetraplegia. [15]

The choice of drug is determined, among other things, by the type of seizures and the type of epilepsy. In neonates, phenobarbital plays an important role. After the neonatal period, the drug of first choice is valproic acid. Carbamazepine has a short half-life, phenytoin given with milk is poorly absorbed, lamotrigine is a good choice for a variety of seizures except for severe infantile myoclonic epilepsy. Gabapentin has a favorable side effect profile. Topamate is

effective in focal seizures, especially when combined with lamotrigine. It can also prevent atonic seizures, but side effects limit its use. Vigabatrin develops concentric visual field narrowing in 50% of patients but is recommended in drug-resistant epilepsy. Oxcarbazepine, tiagabine, remacemide and stiripentol are of limited value. West syndrome requires specific therapies, among which are ACTH, steroids, vigabatrin, benzodiazepines, topiramate, and vitamin B6 in various combinations. [20]

Among the surgical methods of treating epilepsy, there are 3 main types of management: resective surgery

resection surgery, disconnection surgery, and neurostimulation. For surgical treatment Patients with drug-resistant epilepsy and with a very severe course are referred.

Another method of non-pharmacological treatment of epilepsy in children with CP is the ketogenic diet. It should be used when antiepileptic drugs have no effect. It should be started in a hospital setting. Initially, we use starvation and then a fat-rich diet with protein and calorie restriction, especially excluding carbohydrates. [21]

50% of children with cerebral palsy and epilepsy have been reported to have seizures despite anticonvulsants. [7]

A study by Latzer et al. (2019) described a predictive model of drug-resistant epilepsy in children with cerebral palsy that is simple to apply in a clinical setting: low Apgar score at 5 minutes, neonatal epileptic seizures, focal epilepsy, and focal slowing on EEG. [22]

Some of the most common side effects of antiepileptic drugs in children with CP include: significant loss of concentration, memory impairment, hyperactivity, headaches, lethargy, weight gain, and severe muscle pain. [23]

It is worth mentioning that epileptic drugs, especially polytherapy, may contribute to increased bone turnover, reduced bone density, and increased risk of fractures in treated children. [24]

Antiepileptic polytherapy is the gold standard of clinical treatment in children with cerebral palsy and is preferred, even if complete seizure control is not always achieved. Because of the increased risk of side effects associated with antiepileptic drugs, they should be used with caution in these children. This is because only close and continuous multidisciplinary cooperation makes good treatment of these patients possible.

Psychosocial development of children with cerebral palsy and epilepsy

The impact of epilepsy and CP on the quality of life not only of the patients themselves but also of their loved ones, should not be forgotten either. Epileptic seizures can lead to a worsening of motor impairment, making rehabilitation therapy more difficult. It can also contribute to

worsening stress for caregivers due to changes in the therapy plan and the child's deteriorating condition. [25], [26]

Mental health problems are more common in children with epilepsy than in the general population and in children with other chronic diseases that do not affect the nervous system. Rates of mental disorders are even higher in children who have both epilepsy and an additional neurological problem. [27]

Children with CP and epilepsy may have problems with social interactions because their condition leads to misunderstandings and negative reactions from other people. This can result in lowered self-esteem and even more fear of interacting and engaging in group activities. Additionally, the fear of having another seizure can further exacerbate these problems, leading to further isolation. [28]

The mental health of these patients should not be underestimated, as they are more prone to anxiety and depression. This, in turn, causes complications in therapy and hinders daily functioning. It is important to create a supportive environment for these patients and provide psychological/psychiatric care. Addressing emotional well-being can contribute to greater motivation and willingness to face challenges. [29], [30]

SUDEP - Sudden Unexpected Death in Epilepsy

SUDEP is a serious threat to people with epilepsy, including children with CP. Although the literature on SUDEP in children with CP is limited, there is general information on SUDEP that may help understand this risk.

SUDEP is a death in a patient with epilepsy that is not caused by trauma, drowning, an epileptic condition, or other known causes, but for which there is often evidence of an accompanying seizure. It is the leading cause of death in patients with epilepsy. [31]

SUDEP has been reported at various ages, in both children and the elderly. However, the highest incidence has been observed in those between the ages of 20 and 45. [32] A higher risk factor for SUDEP has been reported in patients with epilepsy beginning in childhood, refractory to treatment, and also in men (OR = 1.42). [33]

Other risk factors include a high frequency of generalized tonic-clonic seizures, a long duration of illness, the presence of nocturnal seizures, and polytherapy. [34]

As with other diagnoses, children with epilepsy and their families should be informed about the risks associated with their condition, including SUDEP. Honesty and trust are the cornerstones of the patient-doctor relationship. The literature confirms that parents want to receive accurate information about their child's condition. [35]

Summary

Epilepsy is a common comorbid condition in children with cerebral palsy (CP), which poses a significant clinical problem due to the variety of symptoms and difficulties in diagnosis. The purpose of this article was to present the current state of knowledge on epilepsy in children with CP, including epidemiology, pathophysiology, seizure classification, diagnosis, and treatment. Epidemiologically, epilepsy occurs in 33-39% of children with CP, with a higher risk in children with tetraplegia. Risk factors include both prenatal and postnatal brain damage, including perinatal hypoxia, and comorbidities such as intellectual disability. Studies indicate that epilepsy in children with CP has a different prognosis depending on the type of paralysis, with better outcomes in spastic diplegia.

The pathogenesis of epilepsy in children with CP is complex, and brain damage is central to the onset of seizures. The classification of seizures indicates the diversity of seizure types, which underscores the need for an individualized approach to diagnosis and treatment. Diagnosis is based on medical history, EEG studies, and neuroimaging, which reveal numerous structural abnormalities of the brain.

Treatment of epilepsy in children with CP may include monotherapy or polytherapy with first- and second-line drugs, depending on the type of seizures. In some cases, surgical approaches and a ketogenic diet are necessary. Multidisciplinary cooperation is crucial for the effective management of epilepsy and improving patients' quality of life. Attention should also be paid to psychosocial aspects, as children with CP and epilepsy are more likely to have mental health problems, which can affect their social interactions and overall well-being.

In terms of patient safety, the risk of sudden unexpected death associated with epilepsy (SUDEP) is also an important issue, which poses a serious threat to people with epilepsy, including children with CP. Educating parents and caregivers about this risk is key to providing better care and understanding of the child's condition.

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