Eastern Journal of Medicine 17 (2012) 166 -170

Review Article

Epilepsy in children with cerebral palsy

Maja Jekovec-Vrhovsek

Department of Child, Adolescents & Developmental Neurology, University Children´s Hospital, Bohoriceva, Ljubljana, Slovenia

Abstract. Cerebral palsy (CP) is one of the most common neurologic disorders in children, often complicated with other disabilities. Epilepsy (EPI) and learning disability (LD) are most common in these children. EPI complicates CP in 14-94%, depending on different type of CP being most frequent in tetraparetic children. Managing EPI in children with CP should follow general principles of treating EPI with special attention on possible side effects of antiepileptic drugs (AEDs) or others drugs used for relieving symptoms or commorbidities. The paper is reviewing current information, dealing with epidemiology of both disorders, etiology, diagnosis of EPI in CP children and discuss general principles of therapy.

Key words: Cerebral palsy, epilepsy, learning disability, antiepileptic treatment, side effects, spasticity, quality of life

1. Introduction

Hippocrates was the first who described the seizures and other neurologic conditions in children. After hundreds of years – in the 19th century characterization of the clinical and pathological aspects of the cerebral palsy (CP) played a major role. It had become clear that CP could be the result of pre-, peri-, or postnatal causes, and the role of birth trauma in the production of neonatal brain injuries was recognized (1). Freud recognized higher risk of epilepsy (EPI) in CP patients., the role of EPI as an adverse factor for cognitive function in children with hemiplegic CP has been assessed twenty years ago (2). It is a group of disorders with gross motor function involvement to varying extent being a shared characteristic (3).

CP is a chronic disorder of movement and posture caused by a non progressive brain lesion. CP manifests itself in many ways, causing spastic, dyskinetic, dystonic, ataxic and mixed palsies (4,5).

It is in many ways the prototype for developmental disabilities. By definition the problems stem from one of the main impairments of the developing central nervous system (6) are usually caused by some amount of injury to the brain or head before, during, or shortly after birth. Since the disorder is caused in this manner, many people with CP suffer from seizures as well (7). People with CP are considerably more likely to have also functional difficulties unrelated to movement but related to their central nervous system including sensory, epileptic, learning, behavioural, and related developmental impairment (8). EPI and LD are seen most frequently between them (9).

Relationship between EPI, LD and CP are: early onset of seizure and multiple seizure types, high initial seizure frequency, the increase of incidence and drug resistance of EPI in patients with both severe LD and CP, lower remission rate in long- term follow-up studies in the group of children with severe LD. In some studies there is higher recurrence of seizures after withdraval of AEDs in individuals with lower IQ, although there is no definite correlation between the degree of LD or neurological status and the control of EPI (10).

*Correspondence: Maja Jekovec-Vrhovsek
Department of Child, Adolescents &Developmental Neurology, University Children´s Hospital, Bohoriceva, 20
1525 Ljubljana, Slovenia
phone:+386.1.5229.261
fax: +386.1.5229.357
E-mail: maja.jekovec@guest.arnes.si

2. Epidemiology

CP is the most common form of chronic physical disability in childhood; prevalence is variable and estimated at 2-4 per 1000 (11,12). EPI is one of the most common neuroimpairments in childhood, with a prevalence of approximately 1% in the general population. Although there is some conflict in the literature, it appears that the

prevalence of EPI in children and adults with CP is between 15-55% (13). If only LD coexists epilepsy is found in 3-18% of mildly mentally retarded and up to 50% or even more in severely LD. If CP and LD coexist, the risk of epilepsy in children with CP rises up to 94% depending on CP type and commorbidities (2). The risk remains elevated at least through the first 20 years of life (13).

Different studies confirmed that the onset of EPI in the first year of age was higher in CP children compared to the control group (47-70%), neonatal seizures appeared in about 20% of CP. Status epilepticus was nine times higher in CP children. This group had eight times higher percentage of treatment with politherapy. The CP group had lower incidence of generalized seizures as well as lower seizures free interval frequency (7,14).

2. 1. Epilepsy and cerebral palsy

Motor difficulties, intelectual disabilities and complicating seizures are likely to stem from the same underlying pathology. Seizure disorders take place when there is some overactivity or misdirected activity of electricity in the brain. People with CP can also develop some forms of EPI. People who develop EPI and have CP, usually have a much more variable rate of exhibiting symptoms (2,7). Some studies (15) suggest that cerebral malformations are likely when prenatal events are a predisposing factor for both EPI and CP. There are many different types of malformations: agenesis of the corpus callosum, cortical dysplasias including lissencephaly, unilateral megaencephaly, neuronal heterotopias, lesions associated with tuberous sclerosis, neurofibromatosis type I (16).

When perinataly aquired lesions are present, encephalomalacia, periventricular leukomalatia or diffuse atrophy are found in about half the cases.

During early life, an inadequate oxygenation can lead to structural cerebral abnormalities which relate to the maturational stage of the brain at the time of the insult. Other less common potential causes of both EPI and CP include pre- and perinatal infections- and chromosomal anomalies.

Postnatal lesions that may lead to both CP and EPI are: head trauma, severe intracranial infections, hypoxic injury, stroke. In fact, when associated with LD and CP, they may carry an even higher risk of EPI development than LD and CP from antenatal and perinatal etiologies (13).

In hemiplegic CP; if the lesion is aquired postnataly, the risk of EPI increases (17). EPI can be an estimation of the severity of neurological injury (tetraplegic CP) or cortical injury (hemiplegic CP) (18). On the other hand EPI might be one of the earliest warning signs of CP (as developmental delay, toe walking, persistent fisting, microcephaly, early handedness indicating hemiparesis) (19).

2. 2. CP types and EPI

Children with tetra- or triplegic CP are presumably the most likely to have EPI being affected in between 50-94% (20-22). Different studies estimated from one third to one half of EPI associated with hemiplegic CP children. However children with spastic diplegia have lower risk for developing epileptic disorder because their pathology predominantly involves the periventicular white matter (23,24). Spastic or ataxic diplegia bring some lower risk (16-27%) (25-27). Children with dystonic-dyskinetic CP are affected in one quarter of cases. EPI only rarely complicates pure ataxic CP. Most common are focal seizures, that might be secondarily generalized (28).

3. Diagnosis

The diagnosis of epileptic disorders depends on seizure description. When LD coexists, it is still more important to obtain the description from the parents, nursing staff and others (29). Although the diagnosis of EPI in CP children should follow general diagnostic principles for describing seizure patterns, it might be sometimes difficult to distingush epileptic events from other involuntary movements, particularly in dystonic/dyskinetic or ataxic CP. Children with CP may have breath- holding spells, reflex anoxic attacks, vasovagal syncope, and other types of non- epileptic paroxysmal events (2). Clusters of seizures, prolonged seizures and epileptic status are more commonly seen in multiply disabled and in people with LD, and require special attention (22,27).

4. Electroencephalograpy (EEG)

EEG recording is of great help in confirming the diagnosis of EPI. The studies suggest it should be done without any sedation measures if it is possible (30). Startle epilepsy, observed very frequently in CP children should be considered as a distinctive epileptic syndrome or a particular electro-clinical evolution in patients with a large unilateral brain lesion associated with provoked reflex seizure usually refractory to AEDs (31). It is important to recognize the possibility that subclinical seizure discharges may contribute to cognitive disturbances requiring particular

attention in any child whose abilities may be already impaired due to structural brain abnormalities (2). It has been proposed that treating interictal epileptiform discharges in CP patients without clinical EPI can effectively improve their prognosis and quality of life (6).

5. Neuroimaging

Neuro-imaging technics especially magnetic resonance are of great value to discover possible underlying structural damage (2). Magnetic resonance imaging (MRI) is more likely to be abnormal in cases of CP due to prematurity compared to MRI in children born at term. It is recommended when the etiology of CP has not been established.

It is preferred to computed tomography scan because of its high value in suggesting the etiology and timing of the underlying lesion. (32)

6. Therapy

Seizures are very likely to recur after they have started, so treatment with AEDs should be introduced especially when there are epileptic discharges in EEG (31). Sodium valproate is a good first choice for the epilepsies after the neonatal period (with the exception of West syndrom). Before prescribing it to a young child with disability, a metabolic disorders especially that involving the urea cycle or carnitine metabolism should be excluded. Vigabatrin is very useful in treating West syndrom but concentric visual field defects as side effects tend to limit its usefullness. Phenytoin is difficult to use because of its saturation kinetics and its poor absorption if given orally with milk feeds. Others older drugs (e.g. barbiturates) are used less common. Several new AEDs have improved the ability to control the seizure in these children (23, 24). Topiramate is very efficient in controlling partial seizures. Some side effects (anorexia and weight loss) are undesirable in children with CP. Lamotrigine is succesfull in treating tonic, atonic, myoclonic seizures and absences. The ketogenic diet is experiencing new popularity (2,33). In cases of intractable EPI epileptic surgery should be considered (34).

7. Main side effects of AEDs and drug interaction in treating EPI in children with CP

7. 1. Side effects of AEDs on bone mineral density

Studies have confirmed the possible involvement of antiepileptic treatment and immobility due to CP in lowering bone mineral density. However, most data derived from nonrandomized descriptive studies, not based on large population (3). Nevertheless, the bone health in CP children should be followed by a multidisciplinary team and appropriate therapeutical measures should be introduced when needed (vitamin D and calcium supplementation, bisphosphonates). AEDs treatment should take advantage of new drugs that do not lower bone mineral density (35,36).

7. 2. Side effects of AEDs on spasticity

When using some AEDs in CP children it is necessary to be aware of possible side effects that might worsen CP. Dyskinesia and choreoathetosis could be gabapentin related in severely neurologically impaired patients (37-39). There is a report on urinary retention due to clonazepam (40).

7. 3. Side effects of other drugs on seizures

Systemic treatments for spasticity include baclofen, diazepam, dantrolene, tizanidin- alone or in combinations. Baclofen, the most commonly used oral medication in children with generalized spasticity crosses the blood-brain barrier poorly, therefore high doses may be necessary to achieve clinical response. Among its side effects, lowered seizure threshold may complicate the epilepsy (41). Slow drug titration may minimize these side effects. Abrupt withdraval of baclofen can also results in seizures. Some medications that are primarily AEDs can also benefit to some CP patients in muscle spasms and spasticity (benzodiazepins) or relieve pain (carbamazepine) (7). Some other medications may also provoke seizures (e.g. neuroleptic drugs) (29). When treating pain in CP children due to muscle spasm or contributed to surgical procedure, one must be aware of possible resistance to veruconium that may be displayed by some CP children whether or not they are taking AEDs (42). In surgical procedures in the children with CP, anesthesia and peri-operative seizures control also requires consideration (43).

8. Discontinuation of AEDs therapy

It should be tried when possible after patient has been seizure free for at least two years (31). Factors associated with a seizure-free period of one year or more in epileptic children with CP were: normal intelligence, single seizure type, monotherapy, spastic diplegia (14). AEDs discontinuation in patients with spastic hemiparesis is significantly more likely to lead to seizure relapse than in patients with other CP types, but no other factor is yet known to increase the chance of relapse. There are reports of seizure free patients for more than 3 years who could

discontinue therapy (approximately 3 % or even more). About 15% relapsed after a 3-year seizure-free period and subsequent discontinuation of AEDs. Complete control of seizures could also be achieved in patients with CP and EPI. Regardless of the prognosis of seizures, EPI was a major prognostic factor regarding both the presence of LD and the motor development of children with CP (29,44).

9. Conclusion

Handicap in CP children with LD and EPI is most severe in the dimension of physical independence, orientation and increased significantly with duration of seizures. It is more severe when the onset of seizures is early and when secondarily generalized seizures are present (4,32). The children with EPI but without CP or LD have a mild handicap. When CP is added to EPI the handicap score slightly increases. The handicap is more severe when CP or LD or both are added to EPI (32,34). Studies found children with isolated EPI much more handicapped than controls with CP and EPI in the dimensions of orientation and social integration, physical independence, occupation and mobility (45,46). The quality of life in both groups was related to seizure type, being the lowest in individuals with primary or secondary generalized seizures (32). When epilepsy was improved by surgery, the degree of physical independence improved (46).

The primary care physicians and clinicians caring for children with CP should be aware of associated comorbidities especially of possible seizure disorders (7). Clinicians caring for children with CP need to be familiar with the diagnosis and management of EPI in this population, as it is frequent and may seriously complicate CP disorders (4,5,6). A multidisciplinary team is needed for the comprehensive care of children with CP, EPI and LD especially when all of them are severe. Every effort may be a small part in better quality of the multiple handicapped children's life.

References

1. Ashwal S, Rust R. Child neurology in the 20th century. Pediatr Res 2003; 53: 345-361.
2. Wallace JS. Epilepsy in cerebral palsy. Dev Med Ch Neurol 2001; 43: 713-717.
3. Cohen M, Lahat E, Bistritzer T, Livne A, Heyman E, Rachmiel M. Evidence-based review of bone strength in children and youth with cerebral palsy. J Child Neurol. 2009 Aug;24(8):959-67
4. Russman BS. Disorders of Motor Execution I. cerebral palsy. In: David RB (ed) Child and Adolescent Neurology. St. Louis. Mosby 1998, pp 453-468.
5. Colver AF, Gibson M, Hey EN, Jarvis SN, Mackie PC, Richmond S. Increasing rates of cerebral palsy across the severity spectrum in north-east England 1964-1993. The North of England Collaborative Cerebral Palsy Survey. Arch Dis Child Fetal Neonatal Ed. 2000 Jul;83(1):F7-F12.
6. Stanley FJ, Blair E, Alberman E. Cerebral palsies: epidemiology and causal pathways. London: Mac Keith 2000.
7. Jan MM. Cerebral palsy: comprehensive review and update. Ann Saudi Med 2006; 26: 123-132.
8. Breau LM, Camfield CS, McGrath PJ, Finley GA. Risk factors for pain in children with severe cognitive impairments. Dev Med Child Neurol 2004; 46: 364-371.
9. Shapiro BK. Cerebral palsy: A reconceptualization of the spectrum. J Pediatr 2004; 145: 3-7.
10. Eriksson K, Erilä T, Kivimäki T, Koivikko M. Evolution of epilepsy in children with mental retardation: five-year experience in 78 cases. Am J Ment Retard 1998; 102: 464-472.
11. Koman LA, Smith BP, Shilt JS. Cerebral palsy. Lancet 2004; 363: 1619-1631.
12. Johnston MV. Encephalopaties: cerebral palsy. In: Kliegman RM, Behrman RE, Jemson HB, Stanton BF (eds). Nelson Textbook of Pediatrics. (18th ed).Philadelphia. Saunders-Elsevier 2007, pp 2494-2495.
13. D'AmelioM, Shinnar S, Hauser WA. Epilepsy in children with mental retartdation and cerebral palsy. In: Devinsky o and Weatbrook LE, eds. Eppilepsy and Developmental Disabilities. Boston: Butterworth-Heinemann 2001; 3-16.
14. Kwong KL, Wong SN, So KT. Epilepsy in children with cerebral palsy. Pediatr Neurol 1998; 19: 31-36.
15. Nelson KB, Ellenberg JH. Predisposing and causative factors in childhood epilepsy. Epilepsia 1987; 28: 16-24.
16. Curatolo P, Arpino C, Stazi MA, Medda E. Risk factors for the co-occurrence of partial epilepsy, cerebral palsy and mental retardation. Dev Med Child Neurol 1995; 37: 776-782.
17. Uvebrandt P. Hemiplegic cerebral palsy: aetiology and outcome. Acta Pediatr Scand 1988; 34: 65-68.
18. Fennell EB, Dikel TN. Cognitive and neuropsychological functioning in children with cerebral palsy. J Child Neurol 2001; 16: 58-63.
19. McMurray JL, Jones MW, Khan JH. Cerebral palsy and the NICU graduate. Neonatal Netw 2002; 21: 53-57.
20. Crothers B, Paine RS. Seizures and electroencephalography. In: The Natural History of Cerebral Palsy. Classics in Developmental Medicine No. 2. London: Mac Keith Press 1988, pp 1143-1157.
21. Hadjipanayis A, Hadjichristodoulou C, Youroukos S. Epilepsy in patients with cerebral palsy. Dev Med Child Neurol 1997; 39: 659-663.
22. Krägeloh-Mann I, Hagberg G, Meisner C, et al. Bilateral spastic cerebral palsy--a comparative study between south-west Germany and western Sweden. I: Clinical patterns and disabilities. Dev Med Child Neurol 1993; 35: 1037-1047.
23. Hassan A, Jan MM, Shaabat AO. Topiramate for The Treatment of Intractable Childhood Epilepsy. Neurosciences 2003; 8: 223-236.

24. Jan MM, Shaabat AO. Clobazam for the treatment of intractable childhood epilepsy. Saudi Med J 2000; 21: 622-624.
25. Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 1984; 107: 293-308.
26. Forsgren L. Epidemiology: incidence and prevalence. In: Wallace S, ed. Epilepsy in Children. London: Chapman and Hall 1996, pp 27-37.
27. Zafeiriou DI, Kontopoulos EE, Tsikoulas I. Characteristics and prognosis of epilepsy in children with cerebral palsy. J Child Neurol 1999; 14: 289-294.
28. Carlsson M, Hagberg G, Olsson I. Clinical and aetiological aspects of epilepsy in children with cerebral palsy. Dev Med Child Neurol 2003; 45: 371-376.
29. Jekovec-Vrhovsek M, Tivadar I. An attempt to assess the quality of the epileptological service for severely mentally retarded children and adolescents. In Veličković-Perat M, editor. New developments in child neurology. The presentations from the 8th international child neurology congress; 1998 Sep 13-17; Ljubljana. Bologna: Monduzzi editore 1998; 599-602.
30. Jan MM. Assessment of the Utility of Pediatric Electroencephalograpy. Seizure 2002; 11: 289-293.
31. Caraballo R, Semprino M, Cersósimo R, et al. epilepsy. Rev Neurol 2004; 38: 123-127.
32. Ashwal S, Russman BS, Blasco PA et al. Practice Parameter: Diagnostic assessment of the child with cerebral palsy: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2004; 62: 851-863.
33. Pellock JM, Morton LD. Treatment of epilepsy in the multiply handicapped. Ment Retard Dev Disabil Res Rev 2000; 6: 309-323.
34. Jekovec-Vrhovsek M, Tivadar I. Epilepsije pri otrocih z najtežjimi motnjami v razvoju. Med razgl 1998; 37: 307-311.
35. Jekovec-Vrhovsek M, Kocijancic A, Prezelj J. Effect of vitamin D and calcium on bone mineral density in children with CP and epilepsy in full-time care. Dev Med Child Neurol 2000; 42: 403-405.
36. Jekovec-Vrhovsek M, Kocijancic A, Prezelj J. Quantitative ultrasound of the calcaneus in children and young adults with severe cerebral palsy. Dev Med Child Neurol 2005; 47: 696-698.
37. Chudnow RS, Dewey RB Jr, Lawson CR. Choreoathetosis as a side effect of gabapentin therapy in severely neurologically impaired patients. Arch Neurol 1997; 54: 910-912.
38. Norton JW, Quarles E. Gabapentin-related dyskinesia. J Clin Psychopharmacol 2001; 21: 623-624.
39. Palomeras E, Sanz P, Cano A, Fossas P. Dystonia in a patient treated with propranolol and gabapentin. Arch Neurol 2000; 57: 570-571.
40. Caksen H, Odabaş D. Urinary retention due to clonazepam in a child with dyskinetic cerebral palsy. J Emerg Med 2004; 26: 244.
41. Krach LE. Pharmacotherapy of spasticity: oral medications and intrathecal baclofen. J Child Neurol 2001; 16: 31-36.
42. Hepaguşlar H, Ozzeybek D, Elar Z. The effect of cerebral palsy on the action of vecuronium with or without anticonvulsants. Anaesthesia 1999; 54: 593-596.
43. Nolan J, Chalkiadis GA, Low J, Olesch CA, Brown TC. Anaesthesia and pain management in cerebral palsy. Anaesthesia 2000; 55: 32-41.
44. Delgado LD, Riela AR, Mills J, Pitt A, Browne R. Discontinuation of antiepileptic drug treatment after two seizure-free years in children with cerebral palsy. Pediatrics 1996; 97: 192-197.
45. Silanpää M. Epilepsy in children: Prevalence, disability, and handicap. Epilepsia 1992; 33:444-9.
46. Beckung E, Uvebrant P. Impairments, disabilities and handicaps in children and adolescents with epilepsy. Acta Paediatr 1997; 86: 254-260.