BRAIN GROWTH, MENTAL AND COGNITIVE DEVELOPMENT CAN BE INFLUENCED BY SEVERE EPILEPTIC ACTIVITY DURING EARLY INFANCY

HUDA EPILEPTIČNA AKTIVNOST – HIPSARITMIJA – LAHKO VPLIVA NA RAST MOŽGANOV, UMSKI IN KOGNITIVNI RAZVOJ V RANEM OTROŠTVU

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Abstract *Infantile spasms belong to epileptic encephalopathies of early infancy and represent one of the major causes for acquired mental retardation in early childhood. Cognitive and behaviour impairments can be present even after benign course of disease. Cognitive deficits are in correlation with treatment lag longer then one month, the risk of mental retardation increases after three weeks of hypsarrhythmia duration. Recent studies demonstrate a negative influence of epileptic activity on cortical development in critical period of early brain development. Early treatment is associated with favourable prognosis in cryptogenic as in some symptomatic infantile spasms; however, to prevent specific cognitive deficits early therapeutic strategies should be considered.*

Key words *infantile spasms; epileptic encephalopathy; hypsarrhythmia duration; brain growth; vulnerable period; mental outcome; cognitive deficits; infancy*

Izvleček *Infantilne spazme uvrščamo med epileptične encefalopatije dojenčka in kot epileptični sindrom predstavljajo enega glavnih vzrokov pridobljene umske manjrazvitosti zgodnje otroške dobe. Kognitivni in vedenjski primanjkljaji so lahko prisotni tudi pri benignem poteku bolezni. Kognitivni primanjkljaji so v povezavi s zamikom začetka zdravljenja, daljšem od enega meseca od začetka spazmov, tveganje za umsko manjrazvitost pri bolniku pa se poveča že po treh tednih trajanja hipsaritmije. Novejše raziskave potrjujejo negativni vpliv epileptične aktivnosti na razvoj možganske skorje v kritičnem časovnem obdobju zgodnje razvojne faze možganov. Pravočasno zdravljenje je povezano z ugodnejšo prognozo pri kriptogenih kot tudi pri nekaterih simptomatskih infantilnih spazmih; smiselno pa bi bilo razmisliti tudi o uvedbi zgodnjih terapevtskih strategij za preprečevanje specifičnih kognitivnih primanjkljajev.*

Ključne besede *infantilni spazmi; epileptična encefalopatija; trajanje hipsaritmije; rast možganov; ranljivo obdobje; umski izid; kognitivni primanjkljaj; obdobje dojenčka*

Introduction

The term epileptogenic process is used to define a complex biological mechanisms, which may give an epilepsy the potential to progress and result as a severe farmaco-resistant seizure disorder, associated with behaviour, cognitive and/or mental deficits. If such evolution is observed, the term epileptic encephalopathy is used, to describe a condition in which epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function.[1, 2]

Brain's threshold for seizures

Many environmental factors can influence seizure threshold: fever (in children with genetic predisposition), excitement or fatigue, sleep deprivation as well

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as concentration of glucose, calcium or magnesium can play a role in individual's seizure threshold.
Very important factor affecting threshold for seizures is age. Newborns have a high cortical threshold for seizures: despite the fact that their brain has relatively little inhibition, also the lateral connections between cortical neurons are still underdeveloped, synaptic potentials are labile and cells are unable to fire repetitively for prolonged period of time.[3] Therefore newborn cortex is less able to generate and maintain a cortical seizure. As the cortex matures anatomically and physiologically, the threshold decreases and the infant and toddler have increased susceptibility either to febrile or to seizures from other causes.[3, 4]

Infantile spasms i. e. west syndrome

West syndrome(WS) is an age related epilepsy syndrome and represents one of the epileptic encephalopathies of infancy.[5–7] West syndrome begins in the first year of life, usually between the ages 3 to 9 months of age and the seizures always have a very characteristic pattern: a sudden flexion of the body, knees and head, arms extended and this position is held for 1or 2 sec, then relaxed – only to be repeated in a few sec; infantile spasms typically occur such series of 5 to 10, even 20 consecutive spells. They are most likely to occur in the transition between sleep and wakefulness. Infantile spasms (IS) are nearly always associated with hypsarrhytmic EEG pattern and concomitant developmental arrest/delay; when such a trias is observed the term West syndrome is used.[5, 6] Infantile spasms represent one of the major causes for acquired mental retardation in early childhood.

The role of hypsarrhytmia

The severity of hypsarrhytmic EEG pattern, the chaotic activity with spikes, polyspikes and slow waves of very high amplitude, which reflects a complete distortion of electrogenesis, has been recognized decades ago, from the first description of this pattern by Gibbs and Gibbs.[8] Severe mental retardation followed the evolution of infantile spasms in majority of cases, until the treatment with steroids showed the possibility of better outcome in cryptogenic and some symptomatic cases.[9–11] The role of hypsarrythmia itself as the cause of neurodevelopmental deterioration became more recognized in the next ten years.[9–11] Namely, the etiology of WS can be any of various structural, genetic, metabolic or early hypoxic events occurring in early neonatal or perinatal period and resulting in an early brain damage; it is understood that such infants may have some neurological deficits and developmental delay even before the onset of spasms, but the outcome after IS can be much worse compared to infants of same neurological condition but without additional evolution to epileptic syndrome.
Infantile spasms also occur in previously healthy infants with normal neurodevelopment and with no risk factors before the onset of seizures; if no obvious cause can be identified, the term cryptogenic or idiopatic form of IS is used in clinical practice.[12, 13] In these infants the developmental arrest or even loss of already achieved skills is even more obvious. Sometimes a change in infant behavior and loss of visual contact is observed even few days before the spasms onset.[14–16]

Infantile spasms as a model of epileptic encephalopathy

It is well known for decades that regardless of etiology the potential harm of sub-ictal and interictal discharges (epileptiform abnormalities) are one of the major issues in IS.[9–11] As such IS were regarded as one of those epilepsies, where along with seizures their electrical component – hypsarrhytmia – appear to be the main cause of or at least result in permanent intellectual dysfunction.
Because of the stereotypic clinical picture of IS despite various aetiologies, with hypsarrhytmic EEG pattern, infantile spasms as an epileptic syndrome can be regarded as a model of epileptic encephalopathy during the early developmental period – the first year of life.[1]

Early infancy – the vulnerable period of brain development

During the first and second year of postnatal brain development there is an ongoing process of intensive sinaptogenesis,[17] followed closely by functional cortical maturation, which is experience dependent: elimination of over-numbered synapses is well studied in in animals as in humans. For example, lack of oportunity to get visual information in a child with congenital cataract (not operated in time) results in functional blindness, due to unutilized plasticity – a failure to develop proper conections in the occipital cortex.[17–19] Along with frequent seizures, the hypsarrhythmia itself – representing the continuous epileptic activity as a part of epileptic encephalopathy – is the major cause of neurological deterioration.[1] It may lead either to transient inability to process the visual signal in visual cortex as other sensory modalities in the critical time period of functional cortical maturation and to elaboration of abnormal synaptic conections.[15, 20]
Namely, the age at onset of IS coincides largely with the vulnerable period of cortex development with regard to many special cognitive domaines, from elementary visuomotor skills, attention to more complex memory and learning and language aquisition.[21, 22] Even in infants with benign evolution of IS – short period of spasms and hypsarrhythmia due to early treatment and remission, specific cognitive and behavioural impairement could be found at follow up in 40 % of them.[16, 22]
Hypsarrhythmia, a pathognomonic EEG pattern of the syndrome, with a chaotic high-voltage epileptic activity reflects one of the most severe bioelectrical disturbances, due to a disorder of underlying basic

mechanisms – biochemical or neurotransmitter – receptor disorder, which despite impressive advances in the basic sciences still remains poorly understood due to the intrinsic complexity of the developing brain.[2, 3, 6, 8] But from clinical studies it has been known for decades, that the longer the duration of such epileptic activity, the more severe may be the expected deterioration in the neuro-developmental outcome.[9–11, 23]

Etiology of IS, the treatment lag, duration of spasms and mental outcome

Etiology can nowadays be determined in most of the cases with IS; up to 68 % of patients will have signs of brain injury even before they develop spasms. Although the prognosis with regard to seizures, mental and cognitive outcome largely depends on etiology itself, it soon became clear, that early treatment and in particular early remission of spasms and hypsarrhythmia give much better outcome.[9] It can be expected that children with major brain malformations, severe tuberous sclerosis, chromosomopathies etc. have some degree of developmental delay and mental retardation, but after IS their prognosis can be even worse.[9] On the other side, normal mental outcome has been described in cryptogenic (and idiopathic) IS with prompt response to therapy and long lasting remission of seizures.[11–13]

Although the preexisting brain damage remains the most important prognostic factor, the interval between the onset of IS and the initial therapy – so called *treatment lag* has been recognized since the early eigties as important factor with respect to mental outcome.[9, 11, 23, 24]

A treatment lag of one month was described as a limit in most studies: longer treatment lag correlated with a worse mental prognosis.[9, 11, 16, 23] In some infants hypsarrhythmia continues despite the cessation of spasms (transitory remission), which eventually can reoccure later or another type of seizures appeares, implying the evolution of the condition to resistant epilepsy and mental retardation.

Two recent studies addressed the mental outcome in specific etiologic subgroups of IS (tuberous sclerosis complex and Down syndrome) and showed, that the risk of mental retardation increases significantly with a prolonged duration of spasms and prolonged time from treatment onset until remission of spasms.[23, 24] In addition, in patients with IS and Down syndrome significant correlation was found between the treatment lag and the time to cessation of spasms and later developmental quotient.[23]

In order to explore more in detail the impact of hypsarrhythmia duration in weeks on mental outcome, a cohort of 48 children with IS was studied, using a mathematical model with splines. In this study mental outcome was considered a binary variable and its correlation with the hypsarrhythmia duration was analyzed using the logistic regression model. Since the relationship between the log odds for non normal outcome and the hypsarrhythmia duration was clearly non-linear, restricted cubic splines were used to assess the correlation.[25] The analysis showed that after three weeks of hypsarrhythmia the curve of log odds for non normal outcome begin to increase steeply, meaning that the duration of hypsarrhythmia longer then three weeks correlated with higher risk of mental retardation.[26]

It is of note that in this study a short treatment lag i.e. initiation of therapy within one month of the spasms onset was found in 73 % of infants – in half of them (25 cases) even within 2 weeks, which is better then recently reported.[16] The authors presume that due to a relatively short interval from the onset of IS to the start of treatment in the majority of infants in this cohort, s study of shorter time periods (weeks) of hypsarrhythmia was possible.

Cognitive deficits after infantile spasms

The resolution of hypsarrhythmia is considered the essential marker of primary electro-clinical response, together with cessation of spasms, while its persistence has been shown to correlate with cognitive deterioration.[7, 22, 23] Prolonged hypsarrhythmia may either reflect a severe underlying pathology (drug unresponsive cases), or may as well result from a prolonged duration of IS before the initial treatment (the treatment lag). In earlier studies a delay of treatment longer than one month is described in half of the cases[9, 11] but decreased to one third of cases over the last decade, due to greater awarness of public health staff and earlier recognition.[16, 26] The importance of early treatment with regard to cognitive development is now supported by numerous studies.[9–16]

It is understood that in symptomatic IS cases the underlying pathology may itself cause mental retardation, therefore it is difficult to asses a deleterious effect of hypsarrhythmia alone on the brain development. Studies in cryptogenic IS cohorts showed that the treatment lag longer than one month significantly correlated with lower cognitive outcome.[16] But also in early treatment group (within one month) a permanent damage to cognitive abilities, in addition to the underlying pathology, due to the presence of prolonged hypsarrhythmia may result in lower cognitive outcomes.[16, 23] A study by Jambaque[27] found that in cases of infantile spasms due to tuberous sclerosis, a remission of seizures resulted in significant improvement in cognition and behaviour, including autistic features. In this study greater improvement was noted in verbal than in nonverbal abilities.[27] Recently, a clinical study about the possible influence of epileptic disorder *per se* on the developing brain has been published, in which impaired visual function during active West syndrome was documented, and persistent hypsarrhythmia (in drug unresponsive cases) was related to low scores in visual function two months after the onset of spasms.[28]

In children with normal or borderline mental outcome after IS, specific cognitive deficits may remain unrec-

ognized for a long period of time, often until school age. The possibility of early intervention with specific cognitive therapy came into awarness, as some recent studies demonstrated the beneficial influence of early experience on brain development.[21, 29]

Brain growth and epileptic encephalopathy

Brain growth in an infant is reflected in the rate of the head growth, which can be measured as head circumference (HC) and followed at regular intervals by pediatrician in order to assess normal growth and development in a child. Abnormal growth curve is seen early in infants with co-morbidity which itself influences the rate of head growth (hydrocephalus, Down syndrome etc.)

HC correlates with the brain growth; it closely reflects the relationship to weight, volume, cellular growth and protein content of the brain.[30] A study of a HC in children with IS, compared to normal children in the first and second year of life demonstrated lower HC curve in infants with IS in comparison to normal population from the age of three months on, which corresponded to the age at onset of IS in earliest cases.[31]

The inadequate head growth was found also in cryptogenic IS cases, with the difference between the expected and measured HC being documented from the age of onset of IS. After a certain period, the curve of head growth in infants with cryptogenic IS followed its natural course, but remained on a lower percentile, supporting further evidence that the epileptic activity may have a negative influence on the brain growth.[31]

The head growth is most rapid in the first six months of life hence any negative influence on brain growth quickly becomes obvious. The onset of IS has a peak from the age of 4 to 7 months[5] i. e. during the interval of rapid head growth. A transient deceleration in head growth at the onset of spasms later head growth »catches up« in infants with a favorable outcome. This data demonstrate that there is a transitory disturbance in brain growth during the period of spasms, which seems to be reversible to some extent.[31]

Further investigations are needed to determine whether this is due to the specific treatment (steroid, gabaergic) and/or to the fact that severe epileptic activity exerts a negative influence on brain growth in this sensitive period.[32, 33] A sensitive period for the rate of head growth has also been described in infants with a very low birth-weight, in whom the HC measurement at the age of 8 months has been found to be the best predictor for IQ at the age of three and eight years.[34, 35] These data also support the hypothesis of the existence of a »sensitive period« in brain development in the first year of life with regard to further mental development.

In conclusion, all studies stress the importance of short hypsarrhythmia duration in view of mental and cognitive development. Therefore in infants with resistant spasms, a difficult to treat underlying condition implies further diagnostic and therapeutic work-up.

References

1. Dulac O. Epileptic encephalopathy. Epilepsia 2001; 42 Suppl 3: 23–26.
2. Rho JM. Basic science behind the catastrophic epilepsies. Epilepsia 2004; 45 Suppl 5: S5–11.
3. Moshe SL. Epileptogenesis and the immature brain. Epilepsia 1987; 28 Suppl 1: S3–15.
4. Mc.Donald JW, Johnston MV. Physiological and patophysiological roles of aminoacids during central nervous system development. Brain Res Rev 1990; 15: 41–70.
5. Roger J, Dulac O. West syndrome: history and nosology. In: Dulac O, Chugani HT, Dalla Bernardina B, ed. Infantile spasms and West syndrome. London: Saunders; 1994. p. 6–11.
6. Commission on Pediatric Epilepsy of the International League Against Epilepsy. Workshop on infantile spasms. Epilepsia 1992; 33: 195.
7. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia 2004; 45: 1416–28.
8. Hrachovy RA, Frost JD, Kellaway P. Hypsarrhythmia: variations on the theme. Epilepsia 1984; 25: 317–25.
9. Lombroso CT. Prospective study of infantile spasms: clinical and therapeutic correlations. Epilepsia 1983; 24: 135–58.
10. Watanabe K. West syndrome: etiological and prognostic aspects. Brain Dev 1998; 20: 1–8.
11. Riikonen R. Long-term outcome of West syndrome: a study of adults with a history of infantile spasms. Epilepsia 1996; 37: 367–72.
12. Dulac O, Plouin P, Jambaque I. Predicting favorable outcome in idiopathic West syndrome. Epilepsia 1993; 34: 747–56.
13. Vigevano F, Fusco L, Cusmai R, Claps D, Ricci S, Milani L. The idiopathic form of West syndrome. Epilepsia 1993; 34: 743–6.
14. Jambaqué I, Chiron C, Dulac O, Raynaud C, Syrota P. Visual inattention in West syndrome: a neuropsychological and neurofunctional imaging study. Epilepsia 1993; 34: 692–700.
15. Guzzetta F, Flavia Frisone M, Ricci D, Rando T, Guzzetta A. Development of visual attention in West syndrome. Epilepsia 2002; 43: 757–63.
16. Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia 2004; 45: 255–62.
17. Bourgeois JP, Goldman Rakić PS, Rakić P. Formation, elimination and stabilization of synapses in the primate cerebral cortex. In: Gazzaniga MS. The new cognitive neurosciences, 2nd edition. Cambridge: The MIT Press; 2000. p. 45–53.
18. Neville HJ, Bavelier D. Specificity and plasticity in neurocognitive development in humans. In: Gazzaniga MS. The new cognitive neurosciences, 2nd edition. Cambridge: Massachusetts Institute of Technology; 2000. p. 83–98.
19. Kuhl PK. Language, mind and brain. Experience alters perception. In: Gazzaniga MS. The new cognitive neurosciences, 2nd edition. Cambridge: Massachusetts Institute of Technology; 2000. p. 99–115.
20. Yamada H, Sadato N, Konishi Y, Kimura K, Tanaka M, Yonekura Y, Ishii Y. A rapid brain metabolic change in infants detected by fMRI. NeuroReport 1997; 8: 3775–8.
21. Guzzetta F. Cognitive and behavioural outcome in West syndrome. Epilepsia 2006; 47 S2: 49–52.
22. Gaily E, Appelqvist K, Rantola-Sorsa E, et al. Cognitive deficits after cryptogenic infantile spasms with benign seizure evolution. Dev Med Child Neurol 1999; 41: 660–4.
23. Eisermann MM, DeLaRaillere A, Dellatolas G. Infantile spasms in Down syndrome – effects of delayed anticonvulsive treatment. Epilepsy Research 2003; 55: 21–7.
24. Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. Neurology 2005; 65: 235–8.
25. Harrell FE. Regression modeling strategies with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.

26. Rener Primec Z, Stare j, Neubauer D. The risk of lower mental outcome in infantile spasms increases after three weeks of hypsarrhythmia duration. Epilepsia 2006; 47: 2202–5.
27. Jambaque I, Chiron C, Dumas C. Mental and behavioural outcome in infantile epilepsy treated with vigabatrin in tuberous sclerosis patients. Epil Res 2000; 38: 151–60.
28. Rando T, Bancale A, Baranello G, et al. Visual function in infants with West syndrome: correlation with EEG patterns. Epilepsia 2004; 45: 781–6.
29. Als H, Duffy FH, McAnulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, Warfield SK, et al. Early experience alters brain function and structure. Pediatrics 2004; 113: 846–57.
30. Ellis M, Manandhar D, Costello A. Head growth and cranial assessment at neurological examination in infancy. Dev Med Child Neurol 2003; 45: 427.
31. Rener-Primec Z, Lozar-Krivec J, Krivec U, Neubauer D. Head growth in infants with infantile spasms may be temporarily reduced. Pediatr Neurol 2006; 35: 197–203.
32. Ikonomidou C, Bittigau P, Koch C, et al. Neurotransmitters and apoptosis in the developing brain. Biochem Pharmacol 2001; 62: 401–5.
33. Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 2003; 993: 103–14.
34. Hack M, Breslau N. Very low birth weight infants: Effects of brain growth during infancy on intelligence quotient at 3 years of age. Pediatrics 1986; 77: 196–202.
35. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991; 325: 231–7.

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