REVIEW ARTICLE

MEDICAL THERAPY IN CHILDHOOD PSYCHO-COGNITIVE PROBLEMS

Karimzadeh P. MD[1],

Firozeh SAJEDI MD

1. Associate Professor of Pediatric Neurology, Shahid Beheshti University of Medical Sciences(SBMU), Pediatric Neurology Research Center,Tehran, Iran
2. Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Corresponding Author:
Karimzadeh P. MD
Mofid Children Hospital,
Tehran,Iran
Tel: +98 21 22909559
email:pkarimzadeh@sbmu.ac.ir

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Abstract

Objective

Neurodevelopmental disability is one of the most common problems of children referred to Pediatric Neurology Clinics. These children may suffer from speech delay, intellectual deficiency and behavioral disorder.

Some patients with neurodevelopomental delay, especially those with intellectual disability and speech problems, have abnormal electroencephalograms, without clinical seizure. It seems that treating these patients with antiepileptic drugs normalizes the EEG, thereby preventing the electrical paroxysmal discharges that could be harmful for the developing brain. Several studies reported the use of Valproate, Lamotrigine and Corticosteroid in suppression of subclinical epileptiform discharges and improvement of developmental behavioral conditions.

In our experiences, oral Na-Valproate was effective in developmental behavioral condition of children with neurodevelopmental delay and elimination of subclinical EEG discharges after 18 months of treatment.

Also we used high dose intravenous methyl-prednisolone in a group of children with neurodevelopmental delay and electrical status epilepticus during slow-wave sleep without clinical seizure. In these children results of the appropriate neuro-metabolic tests and magnetic resonance imaging of the brain revealed no abnormality. Because no underlying etiology could be determined, isolated non convulsive status epilepticus was established. After treatment no significant response was observed in these group of children.

In another study we used Lamotrigine in children with neurodevelopmental delay, abnormal epileptiform discharges but without clinical seizures. Our results revealed Lamotrigine provides effective control of both subclinical epileptiform discharges and behavioral disorder, without improvement in their cognition. Further studies are needed to investigate and confirm the cognitive and behavioral effects of Lamotrigine in children with psychomotor retardation.

Keywords: Pshychobehavioral problem, Cognitive problem, Subclinical electrical discharges, Antiepileptic drugs

Introduction

Global developmental delay is defined as delay in two or more of the following developmental domains: Gross/ Fine motor, Speech/ Language, Cognition, Social/ Personal and Activity of Daily Living (ADL). Global developmental delay, which affects one to three percent of all children typically under the age of 5 years, describes a clinical presentation that has a heterogeneous etiologic profile (1); this term usually

refers to younger children, whereas the term mental retardation is usually applied to older children when IQ testing is more valid and reliable (1). Significant delay is defined as performance two standard deviations or more below the mean on age-appropriate standardize norm testing. Behavior is defined as "anything that an organism does involving action and response to stimulation". The definition implies that human behaviors are the results of interactive processes between the individual and the environment.

Environmental influences such as culture, parental skills and neglect may modify the expression as well as the detection and diagnosis of global developmental delay. Evidence also demonstrates the benefits of early intervention through a variety of programs, and suggests that early diagnosis of a child with global delay may improve outcome. Given the higher incidence of epilepsy and behavioral disorder in children with developmental delay, EEG is often considered an initial evaluation.

Cognitive impairment and Subclinical epileptiform discharges

Interictal discharges can occur silently without apparent simultaneous clinical manifestations. Formal testing during electroencephalographic recording may demonstrate transitory cognitive impairment (TCI) (2). Such cognitive impairment occurs exclusively in direct relation to episodes of epileptiform EEG discharges and must be distinguished from postictal seizure effects.

Existing epidemiological data reveal a low prevalence for cognitive impairment during epileptiform EEG discharges. In one study, 2.2% of the patients referred to a specialized epilepsy center for EEG recording, showed a definite relationship between epileptiform EEG discharges and cognitive impairment (transient cognitive impairment) (3). Short epileptiform discharges of 10 seconds or less in children with or without epilepsy are not noticed by clinical observation of the child. Transitory cognitive impairment (TCI) can often be detected during even brief discharges, including single spikes.

In addition some studies have indicated that such mild effects may accumulate over time (when frequent epileptiform EEG discharges persist over years) and consequently result in deterious effects on stable aspects of cognitive function (4).

Several studies have been performed to show the negative effects of these epileptiform electroencephalographic discharges on the choice reaction time test; short term memory tests (verbal and non verbal) and on school performance tasks such as reading and writing.

Generalized 3-HZ spike-wave bursts lasting at least 3 s are most likely to produce demonstrable TCI, but they can also be found during briefer and even focal discharges. About one-half of children with subclinical discharges will show transient cognitive impairment during these discharges; those with predominantly left-sided discharges are weak in reading skills and those with right-sided discharges are weak in visual spatial tasks (5).

Other studies reported left sided focal spiking more frequently produces errors in verbal tasks, whereas right-sided discharges are accompanied more often by impairment in handling nonverbal material (6).

Increasing task difficulty, up to patients, limit of performance, was associated with increasing susceptibility to TCI.

There are thus complex interactions of epileptiform EEG discharges on cognitive function.

The significance of transitory cognitive impairment accompanying subclinical EEG discharges for every day functioning is uncertain, but there is evidence that subclinical discharges may be accompanied by disruption of educational skills in children (3). In some individuals, suppression of discharges by antiepileptic drugs has demonstrably improved psychological function.

It seems early detection of the cognitive impact of seizure related activity and subsequent treatment may prevent its detrimental impact on cognitive and educational development, and is associated with significant improvement in psychosocial function (6). Suppression of the EEG discharges with antiepileptic drugs, viz. "Valproic Acid" "Lamotrigine" and "Carbamazepine" has been reported to improve cognitive performance in children (7).

Inutsuka and colleagues studied the effect of antiepileptic drugs in 15 patients on the EEG pattern of continuous spike-waves during slow wave sleep (CSWS) in 15 patients. Therapies used included: 1. High dose valproate (VPA) therapy (serum level>100 microg/ml);

2. A combination therapy of VPA and ethosuximide (ESM); 3. Short cycles of high dose diazepam oral or intrarectal DZP,0.5-1 mg/kg per day for 6-7 days); and 4. Intramuscular synthetic ACTH-Z therapy(0.01-0.04 mg/kg per day for 11-43 days). Regarding the initial EEG effect, a remission of CSWS was achieved by high dose VPA therapy in 7 of 15 trials(47%), by the combination therapy of VPA and ESM in 3/7 trials (43%), by short cycles of high dose DZP in 2/4 trials (50%), and by ACTH-z therapy in 2/5 trials (40%). A permanent remission of ESES syndrome was achieved by high dose VPA therapy and/or combination therapy of VPA and ESM in 10 patients (67%)(8).

In the Karimzadeh et al study, following 18 months of treatment, oral Na-Valproate was effective in improving the developmental behavioral condition of children with neurodevelopmental delay and subclinical EEG discharges (9).

In this study we recruited children who had behavioral-cognitive problems, but did not have any organic brain disease and had normal results for paraclinical work up (including Neuroimaging, Genetic, Neurometabolic, Torch, etc). After 18 months of treatments all patients had normal EEG and they showed dramatic improvement in behavioral disorders such as aggressiveness, hyperactivity and attention deficit. Good results were also observed in sleep disorders of these children, who also showed improvement in their cognition and speech performance.

Autistic Regression Syndrome and Subclinical Epileptiform Activity

Subclinical epileptiform activity can generate autistic regression in children with pervasive developmental disorder (PDD). Electrographic status epileptiform in sleep, or continuous spike-wave in slow-wave sleep is a typical feature of acquired epileptic aphasia or Laundau-Klefner syndrome. Subclinical seizures and epileptiform activity, are more common among children with autistic spectrum disorder who experience language regression, especially in those who show this regression after the age of 2 years. It has been suggested that the suppression of subclinical epileptiform activity by the early use of antiepileptic drug (AED) can reverse disorders affecting behavior, cognition and language in these patients.

Studies have been conducted to examine the influence of AED therapy on the clinical course of children with PDD and autistic regression, with epileptiform discharge in their EEG, recorded during sleep. Drugs which could bring complete recovery or significant improvement include: Valproate, Ethosuximide, Clobazam, Oxcarbazepine, Sulthiame, Levetiracetam, Topiramate, Lamotrigine and courses of corticoids or ACTH (10,11).

Hollander and colleagues reported beneficial effects of divalproex sodium in autistic spectrum disorders. They used divalproex sodium in treating core dimensions and associated features of autism; asperger's disorder or pervasive developmental disorders or EEG abnormalities.

Results revealed 71% of patients had sustained response to treatment (12).

Nonconvulsive Status Epilepticus and Neuro-developmental delay

Non convulsive status epilepticus, characterized by continuous epileptiform discharges on electroencephalography without motor or sensory phenomena, is a symptomatic condition related to disease such as epileptic encephalopathy or a metabolic disorder. Children with isolated non convulsive status epilepticus rarely present with global neurodevelopmental delay.

Non convulsive status epilepticus, an epileptic state consisting of a prolonged alteration in mental state or behavior, consists of different syndromes including typical absence status epilepticus, complex partial status epilepticus and non convulsive status epilepticus in patients with learning difficulties. Its diagnosis is dependent on electroencephalography and the syndromes have different prognosis and treatments (13).

Electrical status epilepticus during sleep is characterized by spike-and-wave discharges in non-rapid eye movement sleep.

Childhood non convulsive status epilepticus may occur as an isolated phenomenon. It is rare in infants but it should be kept in mind in differential diagnosis of neurodevelopmental delay. Treatment is useful to prevent the long term complication of the disease such as intellectual and cognition impairment and speech.

Compared to other drugs used in the management of non convulsive status epilepticus, such as Benzodiazepines, Valproate is more effective. Some studies revealed dramatic response with intravenous Na-Valproate in children with global developmental delay and isolated non convulsive status epilepticus (14).

Dirik and co-workers reported an 18-month-old male with isolated non convulsive status epilepticus who presented with global neurodevelopmental delay, which was treated with Valproic acid and the patient began to achieve developmental milestones after treatment (13).

In the Karimzadeh, et al study (under publication), high dose intravenous methyl-prednisolone was used in children with neurodevelopmental delay and electrical status epilepticus during slow-wave sleep without clinical seizure; after high dose Methyl Prednisolone therapy, Prednisolone was administered orally (2 mg/kg daily) for 2 months, which was gradually withdrawn. In these children, results of appropriate metabolic tests, and magnetic resonance imaging of the brain revealed no abnormality. Since no underlying etiology was determined, isolated non convulsive status epilepticus was the diagnosis. No significant response was observed with administration of high dose methyl prednisolone in these children; after treatment, 30% of patients showed suppression of electrical status epilepticus during sleep, of whom only 7% showed improvement in cognition and their verbal communication. Among the remaining (70%) we had neither changes of subclinical epileptiform discharges nor global developmental delay.

Okuyaz reported a 4-year-old female patient with continuous spike and waves during slow-wave sleep not classified as landau-klefnere syndrome, who was treated successfully with high-dose intravenous methylprednisolone therapy. After one week, a dramatic clinical and electroencephaloghraphic response was observed and after withdrawal of corticosteroid therapy, the patient maintained the clinical improvement in behavior. No continuous spike and wave electrical stastus epilepticus during slow wave sleep occurred on EEG for 6 months (14).

ADHD and Subclinical Epileptiform Discharges

Evaluation of children with attention deficit hyperactivity syndromes and subclinical epileptiform discharges without seizure revealed a relation between subclinical epileptiform discharges and cognitive dysfunction. Treatment with Antiepileptic drugs (AED) in these children showed significant effectiveness of AED on attention deficit hyperactivity disorders and electroencephalographic discharges (15).

Treatment

Use of AEDs such as Valproate, Ethosuximide, Clobazam, Oxcarbazepine, Sulthiame, Levetiracetam, Topiramat, or Lamotrigine has been reported. In some studies, Valproate is reported to be more effective than other AED in cognition and behavioral disorder (7), whereas in others, sustained improvement with corticosteroids has been found. In these studies after high-dose intravenous methyl prednisolone, dramatic clinical and electroencephalographic responses were observed. In these children, after the withdrawal of corticosteroid therapy, the patients maintained the clinical improvement in behavior and no spike-wave discharges occurred on routine monthly EEG for the last 6 months (14).

Recent studies reported Lamotrigine, a new Antiepileptic drug, can be efficacious and well tolerated in patients with neurodevelopmental delay and behavioral disorder (16). Several studies have demonstrated favorable effects of Lamotrigine on psychological well-being that were not explained by simple effects on seizure frequency and its severity. In addition positive behavioral effects have also been observed in blinded studies and several open trials for patients with severe mental disability and refractory epilepsy(17,18).

Lamotrigine provides effective control of both overt and subclinical seizures, without adversely affecting cognition. According to the Karimzadeh et al study (under publication) Lamotrigine is used in children with neurodevelopmental delay with abnormal epileptiform discharges in EEG and without active seizures.

Results revealed Lamotrigine provides effective control of both subclinical epileptiform discharges and behavioral disorder, without therapeutic effects on cognition. It is well tolerated but further studies with more extensive psycho-behavioral assessment are needed to evaluate and confirm the cognitive and behavioral effects of

Lamotrigine in children with psychomotor retardation.

Conclusion

Improving the neurodvelopmental disabilities of children referred to Pediatric Neurology Clinics is of critical importance, as such children may suffer from speech delay, intellectual deficiency and behavioral disorder.

Many patients with neurodevelopomental delay especially those with intellectual disability and speech problems have abnormal electroencephalograms, some of these have abnormal EEG without clinical seizure.

It seems that Abnormal electrical discharges in these patients cause very short but recurrent impairment of consciousness, which can inhibit their desirable mental development.

Several studies reported the use of AED may suppresse these subclinical epileptiform discharges and improve of their developmental behavioral conditions.

References

1. Shevel M, Ashwal S, Donley D, Flint J. Practice parameter: Evaluation of the child with global developmental delay, American Academy of Neurology. Neurology 2003; 60:367-380.
2. Fonseca LC, Tredus GM, Lalloni DT. Transient cognitive impairment during generalized or diffuse epileptiform EEG discharges. Arg Neuropsiquiatr 2005 Sep; 63(3B): 817-24.
3. Aldenkamp AP, Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of "transient cognitive impairment" still valid? Epilepsy Behav 2004 Feb; 5 (suppl. 1): 525-34.
4. Aldenkamp A, Arends J. The relative influence of epileptic EEG discharge, short non convulsive seizures, and type of epilepsy on cognitive function. Epilepsia 2004 Jan; 45(1): 54-63.
5. Binnie CD, Kasteleijn-Noist Trenite DG. Smit AM. Interactions of epileptiform EEG discharges and cognition , Epilepsy Res, 1987 Jul; 1(4): 239-45.
6. Binnie CD, Channon S, Marston D. Learning disabilities in epilepsy : neurophysiological aspects. Epilepsia 1990;4 (suppl. 31): 52-8.
7. Kasteleijn-Noist Treinte DG. Transient cognitive impairment during subclinical epileptiform electroencephalographic discharges. Semin Pediatr Neurol 1995 Dec; 2 (4): 246-53.
8. Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders.Brain Dev 2006 June; 28(5):1-6. Epub 2006 Jan 10.
9. Karimzadeh P, Tonekaboni S H, Mahvelati Shamsabadi F. The effects of Sodium Valproate in improving Developmental Delay in Seizure-free children with abnormal electroencephalography. Iranian Journal of Medical Sciences 2009 June; 34(2): 110-115.
10. Garcia-Penas JJ. Antiepileptic drugs in the treatment of autistic regression syndromes. Rev Neurol 2005 Jan 15; 40 (suppl.1); S 173-6.
11. Trevathan E. Seizures and epilepsy among children with language regression and autistic spectrum disorders. J Child Neurol 2004 Aug; 19 (suppl.1): S 49-57.
12. Hollander E, Dolgoff-Kaspar R, Cartwright C, Rawitt R, Novotny S. An open trial of divalproex sodium in autism spectrum disorders. J Clin Psychiatry 2001 Jul;62(7):530-4.
13. Dirik E. Yis U. Hudaoglu O. Kurul S. Nonconvulsive status epilepticus and neurodevelopmental delay. Pediatr Neurol 2006 Sep; 35 (3); 209-12.
14. Okuyaz C, Aydin K, Gucuyener K, Sedaroglu A. Treatment of electrical status epilepticus during show-wave sleep with high-dose corticosteroid. Pediatr Neurol 2005 Jan; 32(1): 64-7.
15. Laporte N. Sebire G. Gillerot Y. Cognitive epilepsy, ADHD related to focal EEG discharges. Pediatr Neurol 2002 Oct; 27 (4): 307-11.
16. Meador KJ, Baker GA. Behavioral and cognitive effects of Lamotrigine. J Child Neurol 1997 Nov; 12 (suppl.1): S 44-7.
17. Binnie CD. Cognitive impairment-is it in evitable? Seizure 1994 Dec; 3 (suppl. A): 17-21, discussion 21-2.
18. Dion MH, Novotny EJ Jr, Carmant L. Lamotrigine therapy of epilepsy with Angelman's syndrome. Epilepsia 2007 Mar; 48(3): 593-6.