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Original Article

The Effects of Sodium Valproate in Improving Developmental Delay in Seizure-Free Children with Abnormal Electroencephalography

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Abstract

Background: Developmental delay is one of the most common problems of children referred to pediatric neurology clinics. While there are reports on rehabilitation and its effects, limited studies are available to delineate pharmacotherapy of such children. Because many children with developmental delay have abnormal findings in electroencephalography, we aimed to treat a group of these children, who were seizure free with sodium valproate to find the effect of sodium valproate in improving the developmental delay.

Methods: We included patients referred to Mofid Children's Hospital for developmental delay who had no organic or brain structural diseases, genetic or metabolic disorders, or intrauterine TORCH infection; however, the patients had abnormal electroencephalograms (without seizure). After clinical, para clinical, and neuroimaging evaluations, the patients were divided into two groups; those receiving treatment with sodium valproate and rehabilitation (experimental group, 25 patients), and those having only rehabilitation (control group, 25 patients). The patients were followed up and assessed at 6, 12, and 18 months after initiation of the study. The data obtained were analyzed using SPSS software.

Results: All patients in the experimental group had normal electroencephalograms after 18 months of treatment. Differences in the scores of developmental quotient in both groups, before and after treatment were significant.

Conclusion: Sodium valproate along with rehabilitation was very effective in the improvement of speech, mental, and behavioral development.

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Keywords ● Developmental delay ● sodium valproate ● rehabilitation ● developmental quotient ● electroencephalogram

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Introduction

Developmental delay is one of the most common problems of children referred to pediatric neurology clinics. Improving their developmental conditions therefore is of great importance. These children may suffer from motor delay, speech delay, intellectual deficiency or global

developmental delay. Many patients with speech delay have very limited social interaction (verbal or non-verbal). Other clinical signs such as stereotype movement, rotators movement, intellectual disability, seizure, normal or high head circumference propound the diagnosis of autism or autistic features.[1-6] In many patients with speech delay and normal motor development, behavioral disorders such as irritability, bizarre behaviors, hyperactivity, and aggressiveness can be observed.

Global developmental delay is the most common problem of children with developmental delay. Some patients have histories of prenatal, perinatal, or postnatal brain insult.

Rehabilitations programs are very expensive and are dependent on the skill and experience of the therapists. Hence the patients' outcome may differ. Available literature lacks sufficient data on the effect of anti epileptic drugs in improving the status of such patients.

Many patients with global developmental delay, especially those with intellectual disability and speech problems, have abnormal electroencephalograms. Although they may have a history of seizure but some are seizure-free and are not on anti-epileptic drugs at present. It seems that treating these patients with anti-epileptic drugs normalizes the electroencephalograms (EEGs) by preventing the electrical paroxysmal discharge that could be harmful for the developing brain. Abnormal electrical discharges in these patients cause very short but recurrent loss of consciousness, which can inhibit their desirable mental development.[4,5]

Previous studies have shown that sub-clinical epileptiform activity can generate autistic regression in children with pervasive developmental disorder. It has been suggested that the suppression of sub-clinical epileptiform activity by the early use of antiepileptic drugs can revert the disorder affecting behavior, cognition, and language in these children. Cases of complete recovery or significant improvement after the use of antiepileptic drugs such as valproate, clobazam, levetiracetam, topiramate, or lamotrigine have been reported.[7]

Several studies showed suppression of sub-clinical discharges with valproic acid improved cognitive and behavioral performance of these children.[8-10] Some cases of complete recovery or significant improvement after the use of antiepileptic drugs such as valproate have been reported.[9] Compared with other drugs used in the management of sub-clinical epileptiform discharges such as benzodiazepines, carbamazepine, oxcarbazepine, or topiramate, valproate has been more effective.[8,10]

The aim of this study was to find the effects of sodium valproate in improving developmental delay in seizure-free children with abnormal EEG while the patients were being rehabilitated.

Patients and Methods

We evaluated the patients referred to Mofid Children's Hospital affiliated to Shaheed Beheshti University of Medical Sciences for neuron-developmental delay. The included patients had significant abnormal findings in electroencephalography. They had no organic or brain structural diseases, genetic or metabolic disorders, or intrauterine TORCH infection. Patients under 2 years old were excluded, because of potential adverse reaction of sodium valproate in this age group. Rehabilitation treatments, sodium valproate and its adverse reactions were discussed with patients or their relatives and all patients provided with a written consent for participation in the study. The study was approved by the Ethics Committee of Shaheed Beheshti University of Medical Sciences. The investigations included serum amino acid chromatography (HPLC), urine amino acid and sugar chromatography, measurement of serum lactate, pyruvate and ammonia levels, thyroid function test, urine organic acids, arterial blood gas test and brain magnetic resonance imaging (MRI).

The study was designed as a numerical randomized controlled clinical trial. Fifty patients were divided into two groups of 25 each as follows:

1- Experimental group, treated with sodium valproate (20 – 40 $mg.kg^{-1}.day^{-1}$) plus rehabilitation programs (occupational, speech, and behavior therapy).

2- Control group, underwent only rehabilitation programs.

All the patients were referred to the same rehabilitation center. Rehabilitation was done for both groups by one rehabilitation team (including physiotherapist, occupational therapist, speech therapist, psychologist, and behavior therapist) and it was done by a blind manner.

All patients in the both groups were matched for age, gender, speech delay, behavioral disorder and developmental quotient (DQ). All the patients, before and after treatments, were evaluated by a pediatric neurologist and a pediatric psychiatrist through a blind manner.

DQ, including fine and gross motor development, language, social interactions, and cognition, were evaluated with the Ruth Griffiths mental scale,[11] by a pediatric psychiatrist. The diagnostic criteria of autism, attention deficit, and hyperactivity have emerged from DSM-IV.[11]

Insomnia, according to the International Classification of Insomnia, 2nd edition (ICSD-2),[12] was defined as difficulty in initiating or maintaining sleep. The Overt Aggression Scale (OAS) was used to rate aggressive behavior in patients.[13] All EEGs were reported before and after treatment by only one pediatric neurologist in a blind manner. Spike waves, poly-spike waves, sharp waves, slow waves, spike and slow waves complex, poly-spike and slow waves complex, sharp and slow waves complex in focal or generalized pattern were considered as epileptiform discharges and considered as abnormal.

All patients were followed up and evaluated at 6, 12, and 18 months during the course of study and data were analyzed using SPSS software version 12.0. Chi square and *t* tests were used to compare the effects of sodium valproate in both groups. P values less than 0.05 were considered statistically significant.

Results

Twenty-five patients (21 boys and 4 girls) with a mean age (±SD) of 6.18±2.14 (range: 2-12) years in the experimental group and 25 patients (20 boys and 5 girls) with a mean age (±SD) of 6.68±2.85 (range: 2-12) years in the control group were included in the study.

In the experimental group before the treatment: all patients had abnormal EEGs, four patients had febrile seizure previously but were seizure-free and were not on any antiepileptic drugs at the initiation of the study, 23 patients had motor delay but when we enrolled them in the study all of them had the ability to sit, stand, and walk appropriately, while all patients in this group had speech delay, 20 patients could speak, whereas 5 patients (aged 2.5, 4, 4.5, 6, and 6.5 years) could not. Also in this group, 23 patients had hyperactivity with attention deficit, 20 had aggressiveness, two had attention deficit without hyperactivity and aggression. All patients had insomnia, five patients lacked all features of activity daily living and could not socially interact with others. These five patients could not speak and on the basis of DSM IV criteria had autism (table 1). DQ for five patients of experimental group was 50-55, for other 6 patients was 60-65, for 10 patients was 65-70, and for the remaining four patients was 70 (table 2).

Table 1: Behavioral disorders in experimental and control groups before the treatment

Groups		Experimental	Control
Hyperactivity	+	23	24
	-	2	1
Attention deficit	+	25	25
	-	0	0
Insomnia	+	25	20
	-	0	5
Inability to ADL	+	5	4
	-	20	21
Inability to social interaction	+	5	4
	-	20	21
Aggressiveness	+	20	21
	-	5	4

P value was not significant in all variables. ADL= Activity daily living

In the experimental group, treatment with sodium valproate after 6 and 12 months showed no significant improvement; however, after 18 months all the patients had normal EEGs and were capable to make sentences.

After 18 months, 14 patients were still hyperactive. Three patients had attention deficits. Insomnia and somnolence persisted in eight patients. Five patients had activity daily living ability and had social interaction with others. Aggressiveness was seen in four hyperactive patients (table 3). DQ scores were 65-70 in three patients, ≥70 in 10 patients and ≥ 80 in 12 patients (table 2).

In the control group, before the treatment all the patients had abnormal EEGs (including significant abnormal epileptic discharges) but they did not have any seizures. All the patients in this group, despite having motor delay, had the ability of sitting, standing, and walking, when they were enrolled. All the patients had speech delay, five patients (aged 2, 2.5, 3.5, 4, and 7.5 years) could not speak (were unable to use any words) at the beginning of the study. Regarding the behavior, 24 patients were hyperactive, and all the patients suffered from

Table 2: Developmental quotient in experimental and control groups (before and after treatment)

Groups	Number	Mean	Standard deviation	t	P value
Experimental (before treatment)	25	61	6.726		
Experimental (after treatment)	25	71.6	7.461	+15.49	<0.0001
Control (before treatment)	25	60	7.071		
Control (after treatment)	25	64	9.128	+5.23	<0.0001

Table 3: Behavioral disorder in experimental and control groups after treatment

Groups		Experimental	Control	P value
Hyperactivity	+	4 (16%)	19 (76%)	<0.0001
	-	21 (84%)	6 (24%)	
Attention deficit	+	22 (88%)	19(76%)	0.4635
	-	3 (12%)	6 (24%)	
Insomnia	+	8 (32%)	20 (80%)	0.0017
	-	17 (68%)	5 (20%)	
Inability to ADL	+	5 (20%)	3 (12%)	0.2347
	-	20 (80%)	22 (88%)	
Inability to social interaction	+	5 (20%)	3 (12%)	0.2347
	-	20 (80%)	22 (80%)	
Aggressiveness	+	4 (16%)	19 (76%)	<0.0001
	-	21 (84%)	6 (24%)	

ADL= Activity daily living

attention deficit. Twenty patients had insomnia, four patients did not have activity daily living ability and showed hyperactivity with aggressiveness (table 1). DQ in seven patients was 50-55, in other seven patients was 60-65, in eight patients was 65-70, and in the remaining three patients was ≥ 70 (table 2).

In the control group after 6 and 12 months, no significant improvement was seen. But after 18 months of treatment decreased paroxysmal activity was seen in EEGs of five patients that was previously reported as abnormal. However, these changes were not significant.

Speech improvement was seen in three patients by using words and increased number of words used. Six patients could speak with sentences.

The number of patients with hyperactivity decreased from 24 to 19, and among those with attention deficit disorder, the number decreased from 25 to 6 (table 3).

Although rehabilitation was not effective in patients with insomnia, it was effective in reducing the number of patients with aggressiveness, from 21 to 19.

DQs in five patients was between 50-55, in four patients was 60-65, and in other eight patients was between 65-70. Five patients had DQ ≥ 70 and the remaining three patients had DQ≥ 80 (table 2).

After 18 months, all of the patients in the experimental group had normal EEGs, while only five patients in the control group showed decreased epileptic discharges in their EEGs. Differences in EEGs between the two groups were significant (P<0.001). A significant difference in the improvement of hyperactivity was seen between the experimental and control groups (P<0.001). No significant differences were seen between the two groups in control of attention deficit (P=0.4635) and activity daily living (P=0.234). Significant differences were observed between the two groups in control of insomnia (P=0.0017), control of aggressiveness (P=0.001) and speech development (P<0.001) after 18 months of treatment (table 3). Significant differences were seen in the DQs of patients in the experimental and control groups before and after 18 months of treatment (P<0.001; tables 2, 4).

Discussion

Normal mental, behavioral, and speech development are dependent on normal central nervous system function. Many abnormal EEGs indicate cognitive and behavioral disorders.[8,14-18]

In the present study, patients with abnormal EEGs were treated with rehabilitation with or without sodium valproate, and re-evaluated after treatment to assess their mental and behavioral status.

After 6 months, no significant difference was seen between the two groups. At the assessment done after 12 months, some differences were seen in the experimental group, but they were not significant, whereas none was seen in the control group.

After 18 months, differences in EEGs between the two groups were significant, a finding that is consistent with the study of Plioplys in 1994.[6]

After 18 months of treatment, a significant difference in the improvement of hyperactivity, control of insomnia, and decreased aggressiveness was seen between the two groups

Table 4: Developmental quotient difference in experimental and control groups (before and after treatment)

Groups	Number	Mean difference	Standard deviation	t	P value
Experimental	25	10	3.22	6	<0.0001
Control	25	4	3.81		

(table 3). No significant difference between two groups in control of attention deficit was seen (table 3). A literature search failed to reveal any studies on associations between hyperactivity (per se), attention deficit, and insomnia and treatment with sodium valproate. Our results regarding aggressiveness were similar to those of Gobbi and co workers.[19]

No significant difference between the two groups was observed in activity daily living after treatment (table 3). Again no related data regarding activity daily living and treatment using drugs was found in literature. A significant difference between the two groups in speech development before and after treatment was seen, a finding similar to that of other studies.[4,17,18]

Significant differences were seen in DQs of patients in the experimental group before and after 18 months of treatment (table 2); in the control group, comparing DQs before and after rehabilitation per se, showed significant difference.

The cognitive impact of epileptiform discharges in the absence of seizure (subclinical epileptiform electroencephalographic discharges) was established as early as 1939, when schwab demonstrated a slowing of reaction time during such episodes, even in the absence of seizure.[20]

Cognitive effects of epileptiform discharges may be very similar to those of short epileptic seizures. So, decreased epileptic discharges in EEG can lead to cognitive improvement and this can lead to speech and behavior improvement. This effect was shown in Aart and colleagues study in 1984.[21]

Consequently, accumulating cognitive impairment and even a decline in IQ scores, are reported in patients with frequent episodes with epileptiform discharges.[22-24]

Overall, while significant differences were seen in all of the above mentioned comparison, the differences between the control group and the experimental group were highly significant. This finding is in agreement with other studies.[5,17,18,25-27]

Conclusion

The use of sodium valproate to treat children with abnormal EEGs and developmental delay, especially when no underlying disease was found, seems to be more effective than the use of rehabilitation alone. Treatment with sodium valproate was very effective in the improvement of speech, mental, and behavioral development.

Conflict of Interest: None declared

References

1 Feigelman S. Growth, Development and Behavior In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF. Nelson text book of Pediatric. 18th ed, Philadelphia: Saunders; 2007. p. 33-100.
2 John H. Menkes, Harvey B. Sarnat. Child Neurology, 7th Ed, Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1280.
3 Fenichel GM. Clinical Pediatrics Neurology: A signs and symptoms approach, 5th ed Philadelphia: Elsevier –Saunders; 2005. p. 414.
4 Aldenkamp AP, Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of "transient cognitive impairment" still valid? *Epilepsy Behav* 2004; 5: S25-34.
5 Shinawi M, Shahar E. Neurodevelopmental Delay associated with nonconvulsive status epilepticus in a toddler. *J Child Neurol* 2001; 16: 215-7.
6 Plioplys AV. Autism: electroencephalogram abnormalities and clinical improvement with valproic acid. *Arch Pediatr Adolesc Med* 1994; 148: 220-2.
7 García-Peñas JJ. Antiepileptic drugs in the treatment of autistic regression syndrome. *Rev Neurol* 2005; 40: S173-6.
8 Hirsch E, Schmitz B, Carreño M. Epilepsy, antiepileptic drugs (AEDs) and cognition. *Acta Neurol Scand Suppl* 2003; 180: 23-2.
9 Lewine JD, Andrews R, Chez M, et al. Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders. *Pediatrics* 1999; 104: 405-18.
10 Kasteleijn-Nolst Trenité DG. Transient cognitive impairment during subclinical epileptiform electroencephalographic discharges. *Semin Pediatr Neurol* 1995; 2: 246-53.
11 Sadock Benjamin James, Sadock Virginia Alcott. Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry, 10th Edition, Pheladelphia: Lippincott Williams & Wilkins; 2007. p. 1391.
12 Anders TF. Sleep disorders in infancy through adolescence. In: Wiener JM, Dulcan MK, eds. The American Psychiatric Publishing Textbook of Child and Adolescent Psychiatry. 3rd ed. Washington, DC: American Psychiatric Publishing, Inc.; 2004: 727-42.
13 Yudofsky SC, Silver JM, Jackson W, et al. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry* 1986; 143: 35-9.

14 Binnie CD. Cognitive impairment during epileptiform discharges, is it ever justifiable to treat the EEG? *Lancet Neurol* 2003; 2: 725-30.
15 Binnie CD, Marstone D. Cognitive correlates of interictal discharges. *Epilepsia* 1992; 33: S11-7.
16 Aldenkamp AP, Beitler J, Arends J, et al. Acute effects of subclinical epileptiform EEG discharges on cognitive activation. *Funct Neurol* 2005; 20: 23-8.
17 Aldenkamp AP, Arends J, Verspeek S, Berting M. The cognitive impact of epileptiform EEG-discharges; relationship with type of cognitive task. *Child Neuropsychol* 2004; 10: 297-305.
18 Tromp Sc, Weber JW, Alden Kamp AP, et al. Relative influence of epileptic seizure and of epilepsy syndrome on cognitive function. *J Child Neurol* 2003; 18: 407-12.
19 Gobbi G, Gaudreau PO, Leblanc N. Efficacy of topiramate, valproate and their combination on aggression/agitation behavior in patients with psychosis. *J Clin Psychopharmacol* 2006; 26: 467-73.
20 Schwab RS. A method of measuring consciousness in attacks of petit mall epilepsy. *Arch Neurol Psychiatry* 1939; 41: 215.
21 Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. *Brain* 1984; 107: 293-308.
22 Brinciotti M, Matricardi M, Paolella A, et al. Neuropsychological correlates of subclinical paroxysmal EEG activity in children with epilepsy. 1: Qualitative features (generalized and focal abnormalities). *Funct Neurol* 1989; 4: 235-9.
23 Niemann H, Boenick HE, Schmidt RC, Ettlinger G. Cognitive development in epilepsy; the relative influence of epileptic activity and of brain damage. *Eur Arch Psychiatry Neurol Sci* 1985; 234: 395-403.
24 Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics* 1997; 99: 560-6.
25 MacMillan CM, Korndörfer SR, Rao S, et al. A comparison of divalproex and oxcarbazepine in aggressive youth with bipolar disorder. *J Psychiatr Pract* 2006; 12: 214-22.
26 Staufenberg EF, Brown SW. Some issues in non-convulsive status epilepticus in children and adolescents with learning difficulties. *Seizure* 1994; 3: 95-105.
27 Cascino GD. Nonconvulsive status epilepticus in adults and children. *Epilepsia* 1993; 34: S21-8.