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# Magnesium valproate in learning disabled children with interictal paroxysmal EEG patterns: Preliminary report

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ABSTRACT

Previous studies have investigated whether routine use of antiepileptic drugs is adequate to improve cognitive abilities in children who are learning disabled not otherwise specified (LD NOS) and who display interictal paroxysmal patterns in the electroencephalogram (EEG) but do not have epilepsy, and the findings of these studies have been controversial. In the current study, 112 LD children without epilepsy were assessed; however, only 18 met the strict inclusion/exclusion criteria in order to obtain a homogeneous sample. These children showed interictal paroxysmal patterns in the EEG, and a randomized, double-blind trial was carried out on them. The children were treated with either magnesium valproate (MgV; 20 mg/kg/day) or a placebo for six months, and differences in WISC subtests, in a computerized reading skills battery (BTL) and EEG recordings were evaluated between groups before and after the treatment period. Performance IQ score and several items of the BTL (rhymes and ordering of words) improved in children who received MgV, whereas no changes were observed in the placebo group. No changes in the number of interictal paroxysmal patterns were observed in any group; however increased EEG currents at 10.92 and 12.87 Hz (alpha band) in posterior regions and decreased currents in frequencies within the theta band (3.90, 4.29 and 5.07 Hz) in frontal regions and at 4.68 and 5.46 Hz in the parietal cortex were observed, suggesting an improvement in EEG maturation.



Children with learning disorders (LD) are a heterogeneous population. Abnormal quantitative electroencephalogram (QEEG) recordings were found in 25–45% of reported cases of LD [6,11,13]. Specifically, increased absolute (AP) and relative power (RP) in delta and theta bands with decreased RP in the alpha band have been observed in the QEEGs of children with LD. In addition, interictal paroxysmal pattern discharges, such as spikes, polyspikes, and sharp waves have been observed in conventional EEG [4,19]. This activity is rarely seen in typically developing children [1,13].

Studies measuring the effectiveness of antiepileptic treatment for reducing attention and learning deficits associated with LD in children who do not experience clinical seizures but do present EEG interictal paroxysmal patterns have relied on very heterogeneous samples without control groups [8,14]. The present study was designed to determine whether MgV decreases interictal EEG paroxysmal patterns and/or improves EEG background activity and performance in a reading skills battery and the Wechsler [23] Intelligence Scale (WISC) in children with LD not otherwise specified (NOS) and who present interictal paroxysmal EEG patterns without epilepsy. Valproate was selected for administration because it has been reported to be less likely than any other antiepileptic drug currently available to produce subjective cognitive side effects [3]. Although more than one hundred children with LD were evaluated the low sample size due to the strict inclusion criteria designed to improve group homogeneity is an important limitation of the study; therefore is considered a pilot study that requires replication.

This study was approved by the Ethics Committee of the Children and Women's Specialties Hospital in Queretaro, Mexico. All participants were volunteers and children and parents were informed of the goal and methods of the study, including the information that it was a blind control study and therefore some children will receive placebo and others will receive MgV as well as the

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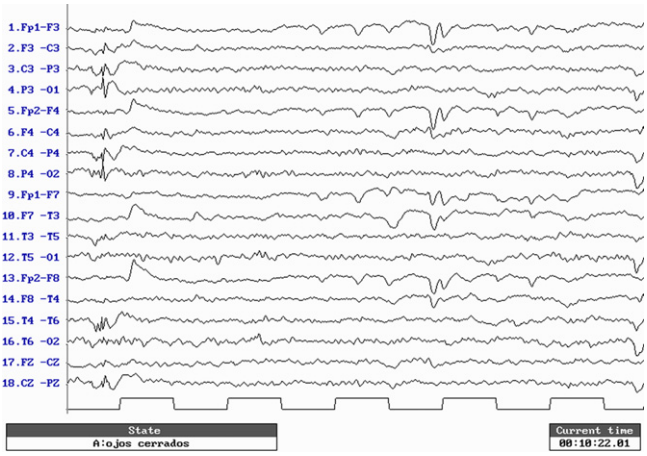


**Fig. 1.** A segment of resting EEG (awake, eyes closed) from a female control child aged 8.9 years that shows multifocal interictal paroxysms: spike wave complex (2.2 Hz) on the P3 lead and polyspikes on the T6 lead. The vertical calibration line at the bottom of the figure is equal to 130 μV, and the horizontal line represents 1-s.

**Table 1**
Demographic characteristics and neuropsychological data obtained through family interview and examination of the child.

| Parameter | Experimental group MgV ($n=10$) | Control group Placebo ($n=8$) |
|---|---|---|
| Age: mean ± SD (years) | 9.4 ± 1.50 | 8.25 ± 2.12 |
| Age range | 6–11 | 6–11 |
| Male/female | 6/4 | 5/3 |
| IQ: mean ± SD (WISC-RM score) | 92.90 ± 19.57 | 95.14 ± 25.09 |
| Number of children with soft neurological signs | 9 | 8 |
| Number of children who have repeated at least one grade in school | 4 | 3 |
| Number of children who have relatives with learning difficulties | 4 | 2 |
| Number of children with a relative with epilepsy | 2 | 2 |

potential risks of using MgV. Written consent was obtained from the parents of each child with previous permission from the child.

An elementary school sent 112 Hispanic children between ages 6 and 11 years with an LD diagnosis to our institute. The children were evaluated by two pediatric neurologists to exclude children presenting epileptic seizures, non-epileptiform paroxysmal disorders, and attention-deficit/hyperactivity disorder (ADHD) as well as children who were taking antiepileptic drugs or stimulants or had visual or hearing impairments. Each patient's clinical history was collected, and a physical exam was performed at the beginning of the study by the same pediatric neurologist who continued with the follow-up of patients during the antiepileptic drug/placebo treatment phase. The pediatric neurologists who assessed the children were blind to the patients' treatment group. To be considered as a candidate for the study, children accomplished the clinical diagnosis of LD NOS consistent with DSM-IV TR criteria [2]. EEG recordings were obtained for all the children and were performed in a quiet environment inside a sound insulated room using digital EEG equipment (Medicid 3E). The child was kept at rest with eyes closed. The EEG recording session lasted 34 min (22 min in a quiet state with eyes either opened or closed followed by 3 min of hyperventilation, 5 min of recuperation, and 4 min of intermittent photic stimulation). The photic stimulation consists of two 20-s trains of light flashes at frequencies of 1, 3, 15, and 30 Hz, with trains separated by 10-s intervals. Nineteen scalp electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz) were set according to the 10–20 International System with earlobe leads as reference. The impedance of the scalp electrodes was less than 5 kΩ. The amplifier's bandwidth was set to between 0.5 and 30 Hz, and the acquisition rate was 200 Hz.

Seventy-nine subjects showed no interictal paroxysmal discharges; consequently, they were not considered for this study. In the remaining 33 children, interictal paroxysmal patterns classified according to the IFSECN [12] as spikes and sharp waves, sharp wave and slow wave complexes, multiple spike complexes, spike-wave complexes (also called spike-and-slow-wave complexes) and polyspike-wave complexes (also called multiple-spike-and-slow-wave-complexes), were observed and counted. Fig. 1 shows a segment of an EEG from a child randomly assigned to the group treated with placebo (control group), and Fig. 2 shows an EEG segment for a child, also randomly assigned, to the group treated with MgV (experimental group).

The intellectual quotient (IQ) of each child in the sample was measured [23], and all children with IQ scores below 75 were excluded. Six children were excluded from the study for this reason. Another 6 children were excluded due to parental refusal to allow their child to participate.

The 21 remaining children were submitted again to pediatric neurological exams, including an exhaustive clinical history, a physical examination, and possible revision of the LD NOS diagnosis. All 21 children met the criteria and were randomly assigned to the experimental (10 children) or control (11 children initially, but 3 abandoned the study) group.

Both groups of children (control and experimental) had interictal paroxysmal EEG patterns [12], including spikes and sharp waves in all the children, multiple spike complexes (25% and 30% of the control and experimental groups, respectively), spikes and slow wave complexes (75% and 50%), sharp waves and slow wave complexes (62.5%, 70%), and polyspikes and slow wave complexes (12.5%, 30%). This activity was focal or multifocal, without preferential lobe or hemisphere localization. No pattern of central-midtemporal spikes was found in either group.

Table 1 describes the characteristics of the control and experimental groups. Age, gender, IQ (before treatment), and other variables of interest for diagnostic purposes are listed. No significant differences in age or IQ were observed between the groups.

The experimental group of 10 children was treated with MgV. The drug was initially prescribed at 15 mg/kg/day for two weeks and during the third week was increased to 20 mg/kg/day until the end of the study. At the beginning of the treatment period, the children underwent weekly clinical follow-ups to adjust the dosage in order to prevent adverse effects. When the children received the 20 mg/kg/day dosages, blood samples were taken for assessment of liver function and MgV concentrations to insure that they remained within therapeutic levels. Serum level and liver tests were carried out three and six months after initiation of the treatment. Subjects also underwent clinical, EEG, and IQ and computerized reading skills evaluations and reevaluations prior to and six months after treatment.

The control group consists of 8 children who were given a placebo for six months. They also received weekly clinical follow-ups at the beginning of the treatment and three and six months after initiation of treatment. Blood samples were also obtained at the beginning of treatment and three and six months after initiation