

Original Research

Magnesium VitB6 Intake Reduces Central Nervous System Hyperexcitability in Children

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Objective: Ionic magnesium (Mg^{2+}) depletion has long been known to cause hyperexcitability with convulsive seizures in rodents, effects that have been reversed by treatment with magnesium (Mg). Metabolic disorders and genetic alterations are suspected in this pathology, in which Mg^{2+} transport and intracellular distribution may be reduced without change in serum Mg^{2+} concentrations. We evaluated the effects of Mg^{2+} /vitamin B6 regimen on the behavior of 52 hyperexcitable children (under 15 years of age) and their families.

Methods: To assess intracellular Mg^{2+} , we measured intra-erythrocyte Mg^{2+} levels (ERC-Mg). Our reference values for normal subjects were 2.46 to 2.72 mmol/L. In 30 of the 52 hyperactive children, there were low ERC-Mg values: 2.041 ± 0.279 mmol/L. Combined Mg^{2+} /vitamin B6 intake (100 mg/day) for 3 to 24 weeks restored normal ERC-Mg values (2.329 ± 0.386 mmol/L).

Results: In all patients, symptoms of hyperexcitability (physical aggressivity, instability, scholar attention, hypertony, spasm, myoclony) were reduced after 1 to 6 months treatment. Other family members shared similar symptoms, had low ERC-Mg values, and also responded clinically to increased Mg^{2+} /vitamin B6 intakes. Two typical families are described.

Conclusion: This open study indicates that hyperexcitable children have low ERC-Mg with normal serum Mg^{2+} values, and that Mg^{2+} /vitamin B6 supplementation can restore normal ERC-Mg levels and improve their abnormal behavior.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) has been described since the beginning of the twentieth century. It impairs millions of people in the world (prevalence 3 to 9%) and is a common chronic and disabling condition in children, that can persist into adulthood. It is characterized by: (i) behavioral disorder with academic and social dysfunction and skill deficit, (ii) high heritability, associated with neurobiological deficits in the prefrontal cortex and related subcortical systems, and (iii) prenatal and perinatal risk factors [1]. Diagnosis is based on the indications of the Statistical Manual of Mental Disorders (IV) classification [1]. The main symptoms are physical aggression with no self-control, instability, inattention which usually ap-

pears at 6 years but can exist at 2 or 3 years at the nursery school. The classical treatment of such disorders includes central nervous system (CNS) stimulants (methylphenidate), tricyclic antidepressants, monoamine oxidase inhibitors and a new compound, atomoxetine. Also, dietetic factors can play a significant role in the etiology of ADHD syndrome, and magnesium (Mg) deficiency might be implicated in hyperactivity in children.

Mg is involved in control of some CNS processes. Mg^{2+} depletion causes hyperexcitability in mice with convulsive seizures [2] that are reversible by administration of Mg^{2+} and vitamin B6. Catecholamines can evoke marked Mg^{2+} efflux, linked to the Ca^{2+} signalling pathway [3]. Two characteristic candidate genes have recently been described: 7-repeat allele of D4-dopamine receptor gene [4]; mutations in TRPM6 gene

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associated with hypomagnesemia with secondary hypocalcemia [5], TRPM6 gene is crucial for Mg transport and homeostasis.

Only one prior clinical study has been reported on the effect of Mg supplementation on hyperactivity in children [6,7]. Reported here is Mg deficiency, indicated by subnormal erythrocyte Mg (ERC-Mg) in 58% of children with ADHD. Significant mental improvement of in the hyperactive children after Mg treatment was associated with increased serum, erythrocyte and hair Mg concentrations after treatment. The aims of this study were to answer the following questions: are low cellular Mg levels associated with ADHD syndrome? Is a familiar incidence in hypomagnesemia associated with ADHD? Is there a place for Mg in the diagnosis and treatment of such disorders?

SUBJECTS AND METHODS

We examined 52 hyperactive children aged 0–15 years old and also members of their family (mother, father, brother, sister). They were mostly from 0 to 6 years old (80%) and were at nursery school. Children fulfilled DSM (IV) criteria for ADHD syndrome, hyperactivity was evaluated with the aid of psychometric scales in relation to their age, the “Connor’s Rating Scale for Parents and Teachers”.

The children were treated with magnesium preparations (Uvimag® or Magne-B6®) at a dose of 6 mg/kg/day for a period of 1 to 6 months.

The blood test for children and their families was the determination of intrerythrocyte Mg^{2+} concentrations (ERC-Mg) by colorimetric assay with chlorophosphonazo III (Roche Diagnostics) after hemolysis and centrifugation. Attention must be taken on hemolysis, many discrepancies in Mg values came from this part of the assay.

ERC-Mg was used to assess intracellular Mg^{2+} . As previously reported, the Mg^{2+}/Na^+ exchanger in erythrocyte was inversely correlated with ERC-Mg [7].

Statistics

Statistical analysis were performed on absolute values, means, standard deviations and standard errors were calculated on each series. For repeated measurements, analysis of variance ANOVA with two repetition factors was used. Comparisons between series were obtained by using the SAS system.

RESULTS

Longitudinal Study

In our hands, reference ERC-Mg values for healthy adult subjects were 2.59 ± 0.72 mmol/L. In the 52 ADHD children ERC-Mg values were 2.041 ± 0.279 mmol/L, significantly different from reference values. A cut-off value was calculated at 2.2 mmol/L (Fig. 1). After 2 months magnesium regimen,

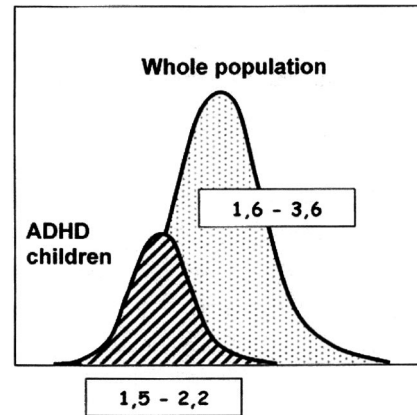


Fig. 1. Repartition of 300 ERC-Mg values in ADHD children and in the whole population of children.

ERC-Mg values for the same 30 children were returned near control values at 2.329 ± 0.386 mmol/L, not significantly different from reference values.

In Fig. 2 the repartitions of ERC-Mg values were reported for children (2.041 ± 0.279 mmol/L) and 37/52 children have values less than 2.2 mmol/L (71%). For mothers, values were 2.155 ± 0.327 mmol/L with 28/43 less than 2.2 mmol/L (65%), for fathers, values were 2.213 ± 0.304 mmol/L with 11/23 less than 2.2 mmol/L (48%).

In a group of 26 children with ERC-Mg values < 2.2 mmol/L, 13/26 mothers have also ERC-Mg values < 2.2 mmol/L, 5/23 fathers have ERC-Mg values < 2.2 mmol/L, and 3/23 children have both father and mother with ERC-Mg values < 2.2 mmol/L.

In addition, 10/26 children have low ionized Ca^{2+} values < 1.18 mmol/L with no correlation between ionized Ca^{2+} and ERC-Mg values.

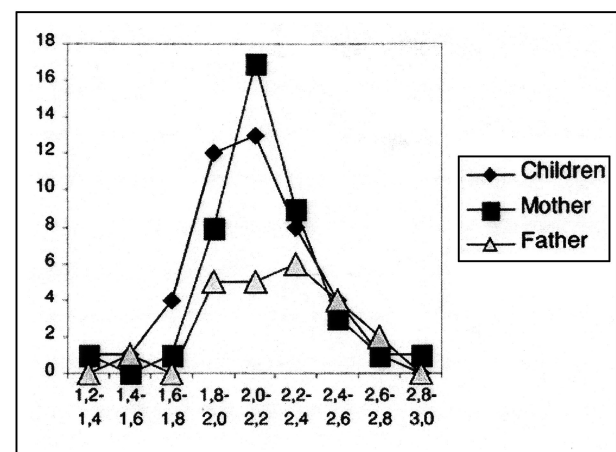


Fig. 2. Repartition of ERC-Mg values for ADHD children (52), their mothers (43) and their fathers (23). It shows that there is a significant shift to the right of ERC-Mg values between the children and their mothers or fathers, however, 50% of the ERC-Mg values were below 2.2 mmol/L in all the three groups.

Table 1 reports the clinical symptoms observed after magnesium treatment. A significant improvement of the main symptom was clearly evidenced after two to four months treatment. In contrast, in severe ADHD with communication disorders, no acquisition of language was evidenced.

Case Report Study 1

This case highlights the follow-up of a typical ADHD patient treated with magnesium. Lud is a boy, born in 1997. He developed a breath-holding spell in his first year, he was hyperexcitable at 3 years, and reports sleep disturbances at 5 years. On 06/01/2003, at the end of nursery school (6 years), the clinical evaluation indicated aggressivity, anxiety, scholar inattention and no self-control. ERC-Mg was 1.86 mmol/L. This child was treated with Mg²⁺/vit B6 and on 19/06/2003 he recovered normal sleep, with no aggressivity, more tender, more concentrated, more quiet; no methylphenidate was needed and ERC-Mg was 2.37 mmol/L. We decided to stop magnesium supplementation.

Case Report Study 2

This case highlights the follow-up of a hyperexcitable family. Jer is a boy, born on 08/05/2001. On 13/09/01 the clinical examination did not reveal any perturbation. On 27/09/01 he was operated on for a hernia and developed bradycardia during anesthesia. On 28/09/01 he presented tonico-clonic convulsions and choreo-athetotic movements on waking up, and the IRM imaging showed fronto-parietal ischemic lesions. A treatment with Gardenal[®] (phenobarbital) and a psychostimulant (Nootropyl[®]) was installed.

In January 2002, a clinical examination revealed axial hypotony but good ERC-Mg was 2.18 mmol/L. A treatment with Mg²⁺/vit B6 was installed. In May 2002, five months later, the boy stood up, played, had normal waking up and a satisfactory

tunus. ERC-Mg was 1.84 mmol/L. In September 2002 he showed a normal wald without any equilibrium disorders and a normal coordination. He began to talk. ERC-Mg was 2.11 mmol/L. Last examination in May 2003, the boy had a normal motility, normal coordination, normal communication and normal electroencephalogram. ERC-Mg was 2.21 mmol/L.

Evaluation of his father disclosed low ERC-Mg (1.88 mmol/L) and hyperexcitability. His mother's ERC-Mg was 2.06 mmol/L, and she had asthenia, but no sign of hyperexcitability. His twin sister had ERC-Mg at 1.68 mmol/L. She was treated for 18 months with Mg. She had normal development with no sign of hyperexcitability; in May 2003 her ERC-Mg value was 2.01 mmol/L. The question was: could the ischemic lesions observed in IRM imaging be attributed to Mg deficiency?

DISCUSSION

There is, as yet, no proof of correlation between ADHD syndrome and intracerebral Mg deficiency. Controlled double-blind studies of Mg therapy, compared with such treatment as methylphenidate or atomoxetine, are critical, since, as previously shown in a few open studies [6,7,9], hyperexcitable children (ADHD) have exhibited low Mg levels. We have shown that ERC-Mg concentrations of ADHD children were below a critical value of 2.2 mmol/L (normal levels being in the range [2.456 B 0.72] mmol/L). These children were, for the main part, at nursery school, and ADHD was diagnosed according to the classical "Connor's Rating Scale for Parents and Teachers" revealing attention concentration disorders, hyperactivity and impulsiveness. The same disturbance was observed in members of their families (more frequently the mother), suggesting a possible genetic origin. Since a genetic abnormality is suspected in this pathology, and mutations in the TRPM6 gene, that is crucial for Mg²⁺ transport and homeostasis, is associated with hypomagnesemia with secondary hypocalcemia, the genetic hypothesis is plausible.

It is not known whether ERC-Mg reflects intracerebral Mg²⁺ levels. However, since the Mg²⁺ exchanger seems to be the same in peripheral blood as in the brain [5], we suspect a correlation between ERC-Mg values and intraneuronal Mg²⁺ values.

In a previous study from Starobrat-Hermelin et al [7], as well as in our study, Mg²⁺/vitamin B6 intake (6 mg/kg/d Mg²⁺ plus 0.8 mg · kg · d vit B6) for 1 to 6 months, partially restored normal ERC-Mg levels and improved the clinical behavior of these children. Our data suggest that the Ca/Mg status may be pertinent in this condition; ERC-Ca²⁺/ERC-Mg values, and relationships with the Ca²⁺/Mg²⁺ exchanger [8] should be investigated.

Table 1. Clinical Symptoms of ADHD Children before and after Mg²⁺/vitB6 Treatment: Number of Children with Indicated Symptoms before and after Treatment, with a Significant Improvement Evidenced even after 4 Months Treatment

Clinical symptoms	Before treatment	After 2 months treatment	After 4 months treatment
hypertony	17/49	11/17	5/17
spasm			
myoclony			
tremors			
significance		P < 0.05	P < 0.001
physical aggressivity	26/49	20/26	6/26
instability			
scholar inattention			
significance		NS	P < 0.01
Developmental disorders	6/49	6/6	4/6
significance		NS	NS

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REFERENCES

1. Spencer TJ, Biederman J, Wilens TE, Faraone SV: Novel treatments for attention-deficit/hyperactivity disorder in children. *J Clin Psychiatry* 63 (Suppl) 12:16–22, 2002.
2. Bac P, Maurois P, Dupont C, Pages N, Stables JP, Gressens P, Evrard P, Vamecq J: Magnesium deficiency-dependent audiogenic seizures (MDDASs) in adult mice: a nutritional model for discriminatory screening of anticonvulsant drugs and original assessment of neuroprotection properties. *J Neurosci* 18:4363–4373, 1998.
3. Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S: Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 238:163–179, 2002.
4. Faraone SV, Biederman J, Weiffenbach B, Keith T, Chu MP, Weaver A, Spencer TJ, Wilens TE, Frazier J, Cleves M, Sakai J: Dopamine D4 gene 7-repeat allele and attention deficit hyperactivity disorder. *Am J Psychiatry* 156:768–770, 1999.
5. Schlingmann KP, Weber S, Peters M, Niemann Nejsum L, Vitzhum H, Klingel K, Kratz M, Haddad E, Ristoff E, Dinour D, Syrrou M, Nielsen S, Sassen M, Waldegger S, Seyberth HW, Konrad M: Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet* 3:166–170, 2002.
6. Kozielec T, Starobrat-Hermelin B: Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD). *Magnes Res* 10:143–148, 1997.
7. Starobrat-Hermelin B, Kozielec T: The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test. *Magnes Res* 10:149–156, 1997.
8. Picado MJ, de la Sierra A, Aguilera MT, Coco A, Urbano-Martinez A: Increased activity of the Mg^{2+}/Na^{+} exchanger in red blood cells from essential hypertensive patients. *Hypertension* 23: 987–991, 1994.
9. Liebscher DH, Liebscher DE: About the misdiagnostics of magnesium deficiency. In *Xth International Magnesium Symposium*, Cairns (Australia), 2003.

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