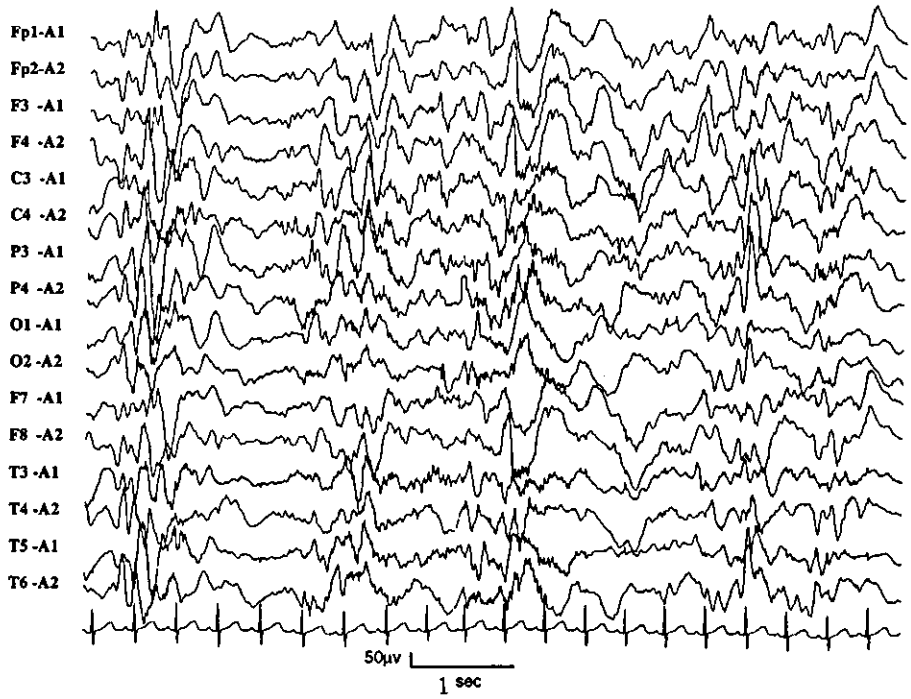

図1 症例1脳波. LS療法前
広汎性棘徐波が繰り返し出現.一部は同期性がなくヒプスアリスミアの所見と考えられた.

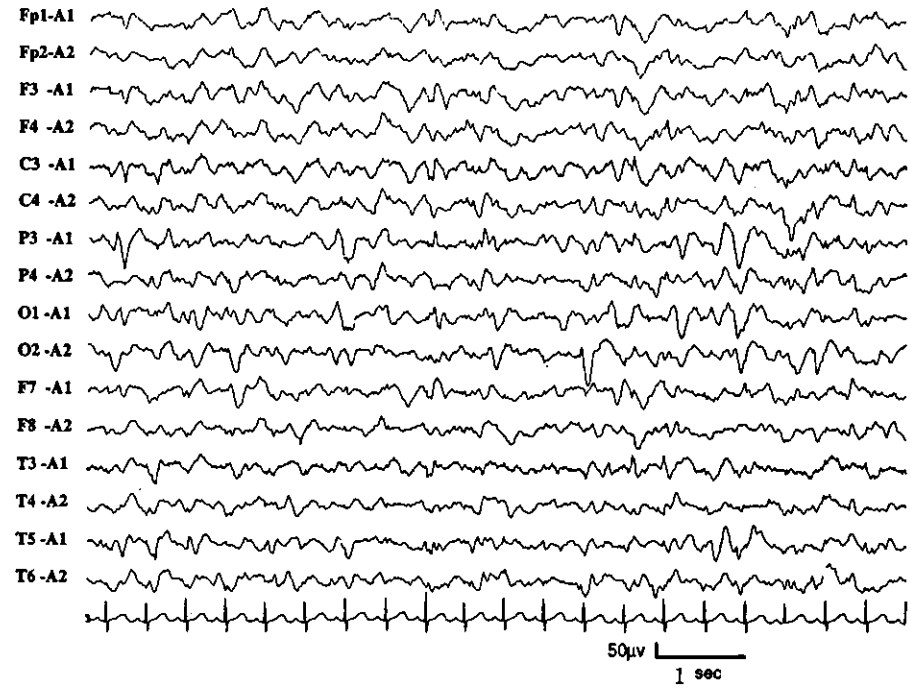

図2 症例1脳波. LS療法後
左頭頂部及び右後頭部に局在性鋭波が残存する.ヒプスアリスミアの所見は軽快している.

認めないかACTH療法に比べ軽度であると一致した結果が得られている. 柳垣らは症候性West症候群9例, 症候性全般てんかん2例, 症候性局在関連てんかん1例の計12例の難治てんかんに対するLS療法の結果を報告している[9]. 彼等はその考察の中で,脳波及び発作の改善を認めた症例においても, 効果発現に4週間以上かかった事を指摘し, 投与量や投与回数の見直しの必要性に言及している. また, 岩井らは[10]ラット

を用いた動物実験においてD-PALとD-PHOSと脳内濃度の測定を行っており，1回の投与のみでは両者に差を認めなかったが，5日間連続投与ではD-PALが有意に高濃度を維持したと報告している．この動物実験の結果からみると，1週間に1回の投与では効果の持続が弱い可能性も考えられる．又，再発率が高い理由として，総投与量の少なさが影響していると考えられた．

これらの事情を考慮し，今回は投与計画を改めLS療法を施行した．症例が少なく，有効性および再発率についての検討は今後症例の蓄積を必要とすると思われたが，ACTH療法後の再発例では効果の低い印象であった．しかし，投与量増量による顕著な副作用の出現はなく，今回の投与方法でも安全に行えると思われた．また，有効例においては4回投与時には発作回数の減少を認めており，効果判定に時間がかかるという欠点は補えていると考えられた．再発率に関しては今後の経過観察が必要である．一方で，今回の投与計画では外来治療が困難になる点が新たな問題と思われた．

てんかんに対するLS療法は，作用機序に関しても不明な事が多く，ステロイドそのものの効果であるのか，あるいは責任病巣に留まる事が効果の増強につながっているのかなど検討すべき課題が多く，従来のステロイド療法との比較も必要であろう．又，適応症例や至適投与方法についての検討もまだ不十分である．しかし，治療抵抗性の難治てんかんや，ACTH療法による重大な副作用が予測されるような症例に対しては，試みる価値があると考えられた．今後も効果及び副作用の両面より，適応症例及び至適投与方法について症例数を増やして検討していく必要があると思われた．

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ELSEVIER

A Successful Treatment With Pyridoxal Phosphate for West Syndrome in Hypophosphatasia

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We report a 2-month-old male with West syndrome associated with infantile hypophosphatasia. The male infant was born at term to a healthy mother after an uneventful pregnancy. He was born by cesarean section because of breech presentation. He was observed to have short extremities, and radiographs were consistent with achondroplasia. The serum alkaline phosphatase level was 2 IU/dL. Intractable tonic seizures developed 2 days after birth, and an electroencephalogram revealed a burst-suppression pattern for the first 2 months of life. The seizures were uncontrollable with conventional antiepileptic drugs. At the age of 2 months, he had a series of infantile spasms, and the electroencephalogram indicated hypsarrhythmia. Treatment with high-dose pyridoxal phosphate eliminated his seizures.

Yamamoto H, Sasamoto Y, Miyamoto Y, Murakami H, Kamiyama N. A successful treatment with pyridoxal phosphate for West syndrome in hypophosphatasia. Pediatr Neurol 2004;30:216-218.

Introduction

Hypophosphatasia is a rare disease marked by subnormal alkaline phosphatase activity in serum and many organs, rachitic bone manifestations, and an increase in urinary phosphoethanolamine. Subnormal serum activity is the hallmark of this disease and reflects a generalized deficiency in the activity of tissue-nonspecific alkaline phosphatase isoenzyme (TNSALP) [1]. It is classified as fetal type, infant type, child type, and adult type, with a more serious and poorer prognosis in the younger patients [2]. We report a 2-month-old male with West syndrome associated with infantile hypophosphatasia. The patient had intractable seizures and a burst-suppression pattern which evolved into hypsarrhythmia in the electroencephalogram. This report is the first case where high-dose pyridoxal phosphate therapy was effective for refractory seizures in West syndrome associated with hypophosphatasia.

Case Report

The patient was born at 38 weeks via cesarean section secondary to breech presentation. During early pregnancy, a twin gestation was evident, but a repeat ultrasound at 11 weeks revealed only one fetus. The remaining pregnancy was uneventful. His birth weight was 2795 gm. After delivery, he had an initial Apgar of 6 and required resuscitation. He had gradually experienced respiratory distress requiring intubation. On examination, he had short bowed extremities and a soft skull. Radiographs were consistent with achondroplasia. His skull was only ossified around the face and forehead, and long bones were short and had metaphyseal cupping (Fig 1). On admission, his serum calcium was 9.5 mEq/L and serum alkaline phosphatase was 2 IU/dL which was extremely low. Increased levels of urinary phosphoethanolamine were identified after hospitalization. His condition was diagnosed as fetal type hypophosphatasia based on the physical examination, radiologic findings, and laboratory findings. Intractable tonic seizures developed 2 days after birth, and the electroencephalogram revealed a burst-suppression pattern for the first 2 months. The cranial magnetic resonance imaging findings were normal.

The seizures were refractory to conventional antiepileptic drugs, such as phenobarbital, phenytoin, clonazepam, and sodium valproate. At the age of 2 months, he had a series of infantile spasms, and the electroencephalogram revealed hypsarrhythmia (Fig 2). In addition, the levels of cerebrospinal fluid γ-aminobutyric acid measured by high-performance liquid chromatography were less than 0.005 nmol/mL. He was diagnosed with West syndrome associated with hypophosphatasia and was begun on high-dose vitamin B_6 (pyridoxal phosphate, 30 mg/kg/day). The seizures decreased remarkably on the day after administration and disappeared by the third day. Electroencephalographic findings at 3 months of age indicated remarkable improvement, and epileptic discharge was not observed (Fig 3). Cerebrospinal fluid examination was performed again

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Received May 15, 2003; accepted August 6, 2003.

doi:10.1016/j.pediatrneurol.2003.08.003 • 0887-8994/04/$—see front matter

Figure 1. The whole-body x-ray reveals profound skeletal hypomineralization.

at the same period, but the levels of cerebrospinal fluid γ-aminobutyric acid were still less than 0.005 nmol/mL which was extremely low. Seizures never recurred, but the patient died of pneumonia at 18 months of age.

Discussion

Hypophosphatasia is a rare metabolic bone disease which highlights the importance of alkaline phosphatase in skeletal mineralization. It is characterized clinically by defective skeletal mineralization that manifests as rickets in infants and children and osteomalacia in adults. Perinatal hypophosphatasia is the most severe form. It is expressed in utero and may result in stillbirth. The pregnancy may also be complicated by polyhydramnios.

Caput membraneceum and limbs that are shortened and deformed from profound skeletal hypomineralization are evident at birth. Radiographic survey of the skeleton enables perinatal hypophosphatasia to be readily distinguished from even the most severe types of osteogenesis imperfecta and congenital dwarfism. Indeed, the radiographic changes may be considered diagnostic. However, the findings are diverse and there is marked patient-to-patient variability [3].

Our patient was diagnosed with perinatal hypophosphatasia. Deficiency of the TNSALP gene is associated with defective skeletal mineralization [4]. Mice that lack TNSALP by homologous recombination with embryonic stem cells have normal skeletal development. However, at approximately 2 weeks of life, homozygous mutant mice develop seizures which are subsequently fatal. Defective metabolism of pyridoxal 5′-phosphate (PLP), characterized by elevated serum PLP levels, results in reduced levels of the inhibitory neurotransmitter γ-aminobutyric acid in the brain. The mutant seizure phenotype can be rescued by the administration of pyridoxal phosphate and a semisolid diet [5]. However, it is suggested that the physiologic role of TNSALP in humans is different from that in knockout laboratory mice [6]. The cause of intractable seizures in hypophosphatasia is still unknown.

In our patient, the levels of cerebrospinal fluid γ-aminobutyric acid were extremely low at the time of initial seizure onset and at the time of the disappearance of seizures; therefore the antiepileptic mechanism of pyridoxal phosphate was unknown. Pyridoxine-dependent seizures associated with hypophosphatasia in an infant were reported by Nunes et al. [7]. The main difference between the present report and the above report is in the development of West syndrome over time and differences between pyridoxine and pyridoxal phosphate. Earlier treatment of the infant in the present report with pyridoxine phosphate would have resulted in clinical reasons identical to those specified in the Nunes et al. report. Litmanovitz et al. reported two missense mutations of the TNSALP gene in

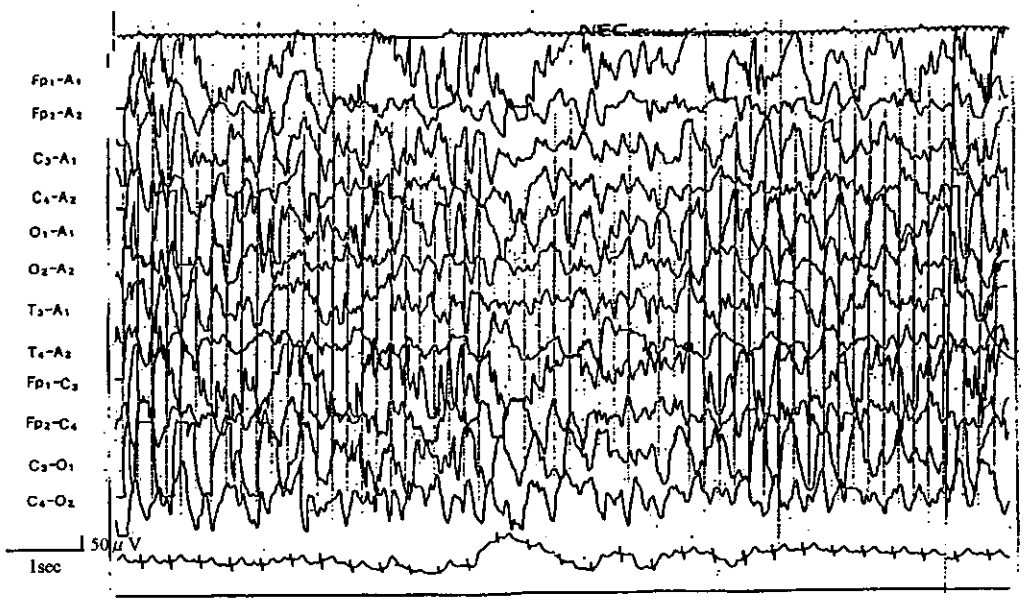

Figure 2. Hypsarrhythmia in the electroencephalogram is observed at 2 months of age.

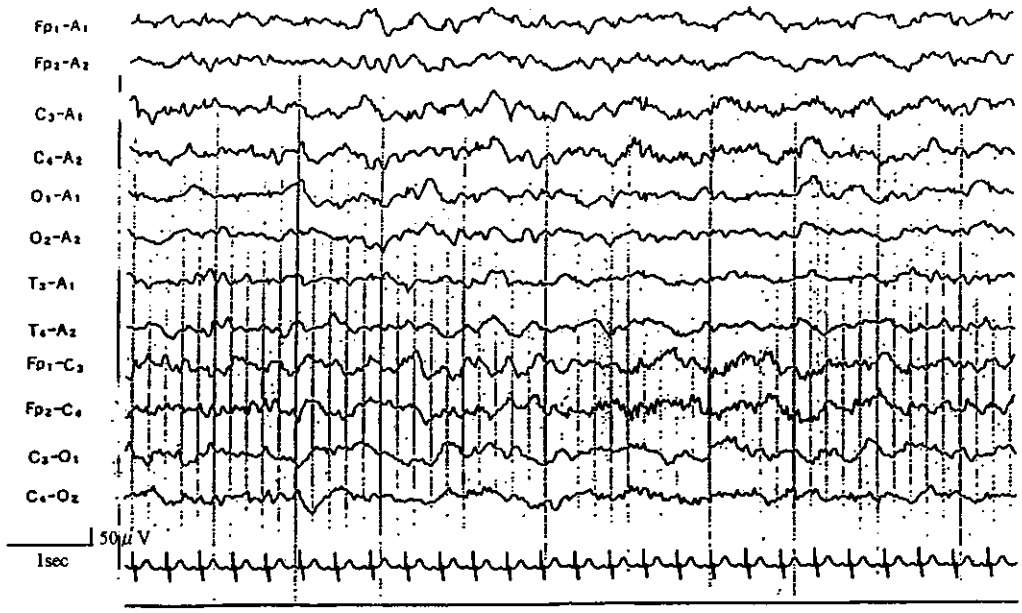

Figure 3. Electroencephalogram at 3 months of age after the administration of pyridoxal phosphate.

neonatal hypophosphatasia associated with seizures [8]. They observed that the seizures responded to vitamin B_6 and stated that the phenotype-genotype correlation indicated that G309R was a deleterious mutation that could lead to seizures and a lethal outcome. The present study is the first case to report the electroencephalographic changes in West syndrome associated with hypophosphatasia by administration of pyridoxal phosphate, and the changes in the levels of cerebrospinal fluid γ-aminobutyric acid during the therapeutic period.

The authors greatly appreciate the expert advice of Professor Takeshi Horiuchi, and also thank Miho Fukuda for her helpful suggestions.

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Pediatrics International (2004) **46**, 394–397

Original Article

Studies on cerebrospinal fluid ionized calcium and magnesium concentrations in convulsive children

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Abstract

Background: The concentrations of ionized calcium (iCa) and ionized magnesium (iMg) were measured in the cerebrospinal fluid (CSF) of convulsive and non-convulsive children, to investigate the relationship between seizure manifestation and CSF iCa and iMg concentrations. Standard concentrations of CSF iCa and iMg were also established.

Methods: CSF samples from 23 patients, ages 0–15 years, with various forms of seizures and 26 age-matched non-convulsive children were collected by lumbar puncture. CSF was obtained anaerobically and the concentrations of CSF iCa and iMg were measured with an electolyte analyzer (Stat Profile Ultra M1, NOVA, USA) immediately after the lumbar puncture.

Results: The concentrations of CSF iCa were significantly higher in non-convulsive children younger than 11 months old compared with children older than 12 months. The concentrations of CSF iMg in non-convulsive children did not differ significantly with aging. The concentrations of CSF iCa in convulsive children did not differ significantly from the concentrations of non-convulsive children. The concentrations of CSF iMg in convulsive children were significantly lower than in non-convulsive children.

Conclusion: These results suggest that seizure manifestation is related to age-dependent changes in iCa and decreased iMg in the developing brain.

Key words acid-base balance, cerebrospinal fluid, convulsion, ionized calcium, ionized magnesium.

Magnesium (Mg) is the second most abundant intracellular cation and the fourth most abundant cation in the body. Mg is a cofactor for more than 325 cellular enzymes involved in cellular energy production, membrane functions, gating of ionized calcium (iCa) channels, transmembrane flux of ions, regulation of adenylate cyclase, and iCa release, inside many types of cells. In addition, ionized magnesium (iMg) has numerous structural functions, stabilizes cell membranes, and acts as a iCa antagonist. Mg plays a role in control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure, among other functions.[1] Ionized Mg acts as a Ca channel blocker and hypomagnesemia presents as tetany or seizures. An increase in pH decreases iMg and iCa activities. Although iMg is affected by a change in plasma acidity (pH), the change is not as large as that for iCa.[2] The H ion competes with iMg and iCa for protein and other ligand binding sites, thereby increasing iMg and iCa activities. A rise in pH results in the reverse, with a drop in plasma iMg. Clinically, certain epileptic seizures can be induced by hyperventilation which raises the pH, and others can be inhibited by a ketogenic diet which lowers the pH. In this study, the concentrations of iMg and iCa were measured in the cerebrospinal fluid (CSF) of convulsive and non-convulsive children to investigate the relationship between seizure manifestation and CSF iMg and iCa concentrations. Standard concentrations of CSF iMg and iCa were also established. This is the first report to study the relationship between CSF iMg and iCa and seizure manifestation.

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Received 22 July 2003; revised 27 November 2003; accepted 27 November 2003.

Materials and methods

Cerebrospinal fluid was obtained from 23 patients, ages 0–15 years (mean 28 months), with various forms of seizures which were the first seizure in their life time, respectively: febrile seizure, seizures following acute gastroenteritis, and situation-related seizures. In total, 26 age-matched (mean

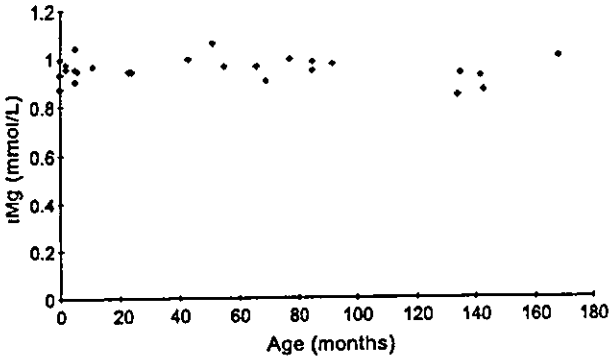

Fig. 1 Concentrations of cerebrospinal fluid ionized magnesium in non-convulsive children.

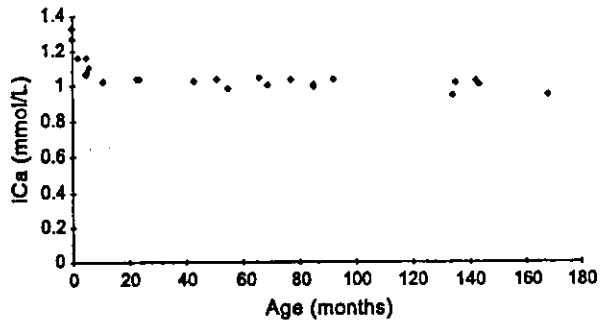

Fig. 2 Concentrations of cerebrospinal fluid ionized calcium in non-convulsive children.

55 months) non-convulsive children's CSF samples were obtained from patients who were examined using lumbar puncture for diagnosis of possible meningitis and then were demonstrated to be normal. None of the controls had any neurological abnormalities. CSF was collected by lumbar puncture anaerobically within an hour after the cessation of seizure activity, from April 2002 to February 2003. The types of seizures were generalized tonic or tonic-clonic, and the duration of each seizure was between 1 and 5 min (mean 3 min). The concentrations of CSF iMg and iCa were measured with an automatic ion selective electrode analyzer (Stat Profile Ultra M1, NOVA, USA) immediately. The concept and inherent advantages of this electrolyte analyzer system have been described previously.[3] The concentrations of CSF iMg and iCa were normalized to pH 7.4 for purpose of direct comparison. This research received prior approval by the University Institutional Review Board, and informed consent was obtained from each patient or parents of each patient in the convulsive and non-convulsive group. The convulsive and non-convulsive children were placed into six groups for analysis. Each of the results was analyzed for the six groups using the Mann–Whitney *U*-test.

Results

The six groups were as follows: Group A, six convulsive children younger than 11 months old; Group B, 10 non-convulsive children younger than 11 months old; Group C, 17 convulsive children older than 12 months; Group D, 16 non-convulsive children older than 12 months; Group E, all 23 convulsive children; Group F, all 26 non-convulsive children. The concentrations of CSF iMg in non-convulsive children did not differ by age and were held within a narrow range (Fig. 1). The concentrations of CSF iCa were significantly higher in non-convulsive children younger than 11 months old compared with children older than 12 months, and after 12 months CSF iCa was also maintained in a narrow range (Fig. 2). The concentrations of CSF iMg in convulsive children older than 12 months were significantly lower than in non-convulsive age-matched children. The concentrations of CSF iCa in convulsive children did not differ significantly from the concentrations of non-convulsive children. These results are listed in Table 1 and Table 2.

Discussion

Extrapolating from Ca studies where iCa, not total Ca was found to be physiologically active, it is anticipated that iMg and not total Mg is also physiologically active. Whole blood maintains a very narrow normal range for iMg.[4] This study revealed that CSF iMg and iCa were also maintained in a very narrow range. Intracellular total Mg greatly exceeds extracellular or serum total Mg concentrations. In contrast, intracellular iMg appears to be quite comparable to extracellular iMg. In addition, iMg passes through the cell membrane relatively quickly suggesting that the two iMg reservoirs are in dynamic equilibrium.[5] These observations suggest that the extracellular measurement of iMg reflects the dynamic intracellular–extracellular Mg homeostasis. Concentrations of neurotransmitters in CSF are determined by the rates of synthesis, release, and degradation of the parent compounds as well as the rate and efficiency of elimination from brain and CSF. Maturational changes in storage pool, rates of turnover, transport systems, intra- and extraneuronal metabolism, rates of CSF production, and brain and spinal column morphology, all may alter CSF neurotransmitter concentrations.[6] In previous studies, several investigators reported that the CSF concentrations of several neurotransmitters in younger children were considerably higher than those of older children and adults.[7] In the present study, no significant correlation was observed between age and the CSF concentrations of iMg. The concentrations of CSF iMg were extremely stable despite age, time, and the volume of CSF taken. In contrast, the present study documented an

Table 1 Concentrations of cerebrospinal fluid (CSF) and ionized magnesium in convlusive and non-convulsive children

	Age ≤ 11 months	Age ≥ 12 months	Total
Convulsive group (n = 23)	Group A (n = 6) 0.96 ± 0.02 a,b	Group C (n = 17) 0.89 ± 0.02 a,d	Group E (n = 23) 0.90 ± 0.01 e
Non-convulsive group (n = 26)	Group B (n = 10) 0.95 ± 0.01 b,c	Group D (n = 16) 0.95 ± 0.01 c,d	Group F (n = 26) 0.95 ± 0.01 e

All data expressed as mmol/L CSF (mean ± SE). Letters indicate significance between values with the same letter: a-c, not significant; d-e, $P < 0.05$.

Table 2 Concentrations of cerebrospinal fluid (CSF) and ionized calcium in convlusive and non-convulsive children

	Age ≤ 11 months	Age ≥ 12 months	Total
Convulsive group (n = 23)	Group A (n = 6) 1.11 ± 0.05 a,c	Group C (n = 17) 1.00 ± 0.01 a,d	Group E (n = 23) 1.03 ± 0.02 e
Non-convulsive group (n = 26)	Group B (n = 10) 1.16 ± 0.01 b,c	Group D (n = 16) 1.01 ± 0.01 b,d	Group F (n = 26) 1.07 ± 0.02 e

All data expressed as mmol/L CSF (mean ± SE). Letters indicate significance between values with the same letter: a, $P < 0.05$; b, $P < 0.01$; c–e no significant difference between groups.

inverse correlation between age and CSF concentrations of iCa. The lower concentrations of CSF iCa after 12 months old may be related to the general increasing seizure susceptibility in children. The importance of age-matched non-convulsive children in studies of CSF neurochemicals in the developing brain is emphasized. However, there is no normal control data for CSF iMg and iCa, and the relationship between seizure manifestation and CSF concentrations of iMg and iCa has not been previously reported in children. Approximately 50% of convulsive and control children had fever at the moment of lumbar puncture and the influence of fever to the measurement results was not clear, but fever has been demonstrated not to affect some CSF neurochemicals.[8]

There is a serial study, by Lux and Heinemann, about the movement of extracellular iCa during the aberrant depolarization of a neuronal cell.[9–12] According to the report, decreased concentrations of extracellular iCa in cortical IV and V layers and in the cone cell blanket of hippocampal CA1 and CA3, were observed using microelectrodes. When the concentrations of intracellular iCa increase after iCa flows into a cell, non-specific depolarizing membrane current is activated and bursting activity occurs. Sugaya *et al.* also reported the relationship between the bursting activities and the inflow of iCa into a neuronal cell.[13,14] There was another report which described the relationship between the urinary concentrations of Ca and febrile convulsions.[15] These results suggest that the dynamics of iCa in neuronal cells play an important role in the seizure manifestation.

Magnesium exists as three forms *in vivo*: protein binding Mg, anion-bound Mg, and iMg. Tissues respond to the ionized fraction of Mg, not the total concentration, where cations may be bound to protein or small ligands.[16] The measurement of iMg in whole blood, plasma or serum has been difficult historically, but became easier in 1992 with the use of ion-selective electrodes.[3] However, there is no report of reference concentrations of iMg in CSF or changes in the concentrations of CSF iMg in convulsive children. Acid-base balance influences the measurement results of CSF iMg and iCa. With increased acidity, H ion enters cells and the charge is balanced by iMg and iCa leaving cells. Alkalinizing results in the reverse, with a drop in iMg. In this study, we collected CSF anaerobically and analyzed it immediately after the lumbar puncture. We normalized iCa and iMg values to pH 7.4 using a correction formula in the instrument to exclude the effects of crying and sample preservation.[17] The concentrations of CSF iCa were significantly higher in control children younger than 11 months old compared with in children older than 12 months. This result suggests that the decreasing concentrations of iCa in the brain may relate to the increasing age-dependent seizure threshold in childhood after 12 months of age. In contrast, the concentrations of CSF iMg did not differ with aging, but the concentrations of CSF iMg decreased after convulsions. These results suggest that the concentrations of CSF iMg are held within a narrow range in normal children. Studies on convulsive subjects indicate that CSF iMg concentrations are significantly lower than normal. In the N-methyl-D-aspartate receptor, which is one of the brain's excitatory neurotransmitter glutamic acid receptors, a glycine binding site, a sodium and Ca ion channel, an Mg binding site, is also implicated. And, it is said that the subunits constituting the glutamic acid receptor, change with age.[18] These results suggest that there is a relationship

between the changes in concentrations of extracellular iMg in the brain and seizures in childhood. Although the differences are statistically significant, the fact that variables (e.g. circadian changes, sex, pharmaceutical influences, and dietary influences) were not controlled, make these findings preliminary. More patients in each range need to be studied.

Acknowledgments

The authors greatly appreciate the expert advice of Terry L Shirey PhD, the director of scientific affairs, NOVA biomedical, and also Professor Yasushi Koitabashi for his helpful suggestions.

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Brain & Development 26 (2004) 377–379

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

Spontaneous improvement of intractable epileptic seizures following acute viral infections

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Received 9 June 2003; received in revised form 4 September 2003; accepted 25 September 2003

Abstract

In general, epileptic seizures become more serious following infections. However, transient and permanent improvement of epileptic seizures has been observed following acute viral infections, without a recent change in anti-epileptic therapy. Questionnaires were sent to 73 institutions, throughout Japan, where pediatric neurologists care for children with epilepsy to characterize this phenomenon through clinician survey. Completed surveys were received from 11 institutions, and 21 cases were selected for the study. The age of the patients were 6 months to 17 years. The West syndrome or epilepsy subsequent to West syndrome cases were 16 out of 21. Two cases of symptomatic generalized epilepsy and one case each of symptomatic partial epilepsy, continuous spike-waves of slow sleep and severe myoclonic epilepsy in infancy were also reported. These seizures disappeared within 2 weeks subsequent to viral infections such as, exanthema subitum, rotavirus colitis, measles and mumps. The disappearance of intractable epileptic seizures following acute viral infections might be related to the inflammatory processes or the increased levels of antibodies after viral infections.

Keywords: Spontaneous improvement; Acute viral infection; Intractable epilepsy

1. Introduction

Epileptic seizures generally become more serious following infections. However, it is well known that in rare instances, epileptic seizures, mostly seizures in West syndrome disappear or decrease in severity after acute viral infections without changes to anti-epileptic medications. This evidence has prompted us to analyze clinical data of this phenomenon through a multi-center survey throughout Japan. The goal of our study was to better characterize this phenomenon through clinician survey.

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0387-7604/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2003.09.012

2. Subjects and methods

Questionnaires were sent to Pediatric neurologists in 73 university hospitals, children's hospitals, and epilepsy centers in Japan. The questionnaires reported: the type of epilepsy or epileptic syndrome according to the international classification of the ILEA, 1989; the infectious disease that the patient experienced; the start of seizure remission in relation to the start of the illness; the duration of remission; any changes in the EEG during the disappearance of seizures; any changes in the serum concentrations of anti-epileptic drugs during the disappearance of seizures; any additional medications given for the illness; recurrence of seizures; and the suspected reasons for the disappearance of seizures.

3. Results

Completed surveys were received from 11 institutions, and 21 cases were selected for this study based on the criteria. The criteria fulfilled the conditions in which patient's frequent seizures had disappeared for at least 1 month after viral infections without changes to anti-epileptic therapy. The age of patients ranged from 6 months to 17 years. The West syndrome or epilepsy subsequent to West syndrome was diagnosed for 16 out of 21 cases. Two cases were symptomatic generalized epilepsy. Symptomatic partial epilepsy, continuous spike-waves of slow sleep (CSWS), and severe myoclonic epilepsy in infancy (SMEI) were reported concurrently in another case. Thirteen patients with either West syndrome or epilepsy subsequent to West syndrome were symptomatic, and three patients were cryptogenic in etiology. The patient's international classification of epilepsy or epileptic syndromes are presented in Table 1. The preceding infections were four cases of exanthema subitum, four cases of rotavirus gastroenteritis, three cases of measles, three cases of upper respiratory infections, one case of mumps and cytomegalovirus infection, and five cases of probable common cold. The type of infectious disease encountered was listed in Table 2. Seizures disappeared an average of 4.5 days, (with a range of 1–14 days) after the onset of infection. In four patients with West syndrome and in one patient with CSWS, the seizures did not recur. The mean duration of follow-up was 34 months with a range from 3 months to 4 years. In 13 patients, the seizures recurred. In these patients, the duration of remission had a median of 7 months and a range from 1 to 30 months. During the remission, the EEG was improved in two-thirds of patients including those with CSWS syndrome. No significant changes were seen in the serum concentrations of anti-epileptic drugs during the remission. Possible reasons for the resolution of seizures in these patients are: (1) an immunologic or inflammatory processes; (2) increased serum concentration levels of anti-convulsant due to dehydration with the illness; (3) increased levels of antibodies after viral infections (similar to immunoglobulin therapy in intractable epilepsies; (4) suppression of immunopathological processes by anti-inflammatory cytokines, such as interleukin-10 and transforming growth factor-β.

Table 1
The classification of epilepsy or epileptic syndromes encountered (*n*)

West syndrome and subsequent epilepsy post West syndrome (16)
Cryptogenic type (3), symptomatic type (13)
Lennox-Gastaut syndrome (2)
Symptomatic localization-related epilepsy (1)
Severe myoclonic epilepsy in infancy (1)
Continuous spike-waves of slow sleep (1)

Table 2
The types of infectious diseases encountered (*n*)

Probable common cold (5)
Rotavirus gastroenteritis (4)
Exanthema subitum (4)
Upper respiratory infection (3)
Measels (3)
Mumps (1)
Cytomegalovirus infection (1)

4. Discussion

Patients with intractable epilepsy in infancy, particularly West syndrome, rarely show spontaneous remission of seizures. This aspect of the natural history of these epilepsies has been insufficiently recognized. Hrachovy reported that spontaneous remission of West syndrome may occur as early as 1 month after spasm onset and the remission rate increased to 25% 12 months after onset without effective therapy, such as adrenocorticotropic hormone (ACTH) or valproate, but author did not describe any events triggering spontaneous remission [1]. The disappearance of seizures most often occurs following a viral infection. West first described in his syndrome a patient with such a remission after a brief febrile illness [2]. Some patients with intractable epilepsy respond to the therapy with immunoregulatory or anti-inflammatory agents such as high-dose immunoglobulin, ACTH or corticosteroids [3, 4]. The participants of the present survey proposed the following mechanisms for the disappearance of intractable epileptic seizures following acute viral infections: increased serum concentrations of anti-epileptic drugs with secondary to dehydration, increased levels of antibodies after viral infections (similar to immunoglobulin therapy), and the suppression of immunopathological processes by anti-inflammatory cytokines, such as interleukin-10 or transforming growth factor-β. Increased vascular permeability of blood–brain barrier under the condition in the intractable epilepsies, such as West syndrome or Lennox-Gastaut syndrome was proposed by Ariizumi et al. [5]. The increased vascular permeability allows immunoglobulins to easily cross the blood–brain barrier following acute viral infections (also similar to immunoglobulin therapy). However, these speculations are not based on the experimental or laboratory data. In this study, we could not find a reasonable explanation as to the relationship between the spontaneous improvement of intractable epilepsies and acute viral infections. In 2002, Hattori identified the spontaneous remission of spasms following acute viral infections in 25 patients with West syndrome on the base of data analysis of Japanese medical literature between 1970 and 2000 [6]. In this study, exanthema subitum was most predominant infectious disease that

leads to resolution of the seizures. He also stated that these spontaneous remissions following acute viral infections have not been duly appreciated in the English medical literature. Better understanding of such mechanisms may lead to a new therapeutic approach to intractable epilepsies in infancy.

The participants in the survey:

- Kimio Minagawa (Otaru)
- Eiji Nakagawa (Tochigi)
- Masatoshi Ito (Shiga)
- Tomiyuki Akiyama (Okayama)
- Harumi Yoshinaga (Okayama)
- Shigeru Yanagaki (Tokyo)
- Mana Kurihara (Atsugi)
- Toshio Hanai (Fukuoka)
- Tomoyuki Nakazawa (Tokyo)
- Toshiyuki Iwasaki (Sagamihara)
- Hitoshi Ueda (Osaka)
- Hiroshi Murakami (Kawasaki)

Acknowledgements

We would like to thank those who participated in the survey.

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Brain & Development 26 (2004) 43–46

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

Hypouricemia in severely disabled children II: influence of elemental enteral nutrition on the serum uric acid levels

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Received 24 October 2002; received in revised form 3 April 2003; accepted 4 April 2003

Abstract

The previous study showed that both valproic acid (VPA) and a bedridden state decreased the serum uric acid level, and VPA-induced renal tubular dysfunction was suspected to be one cause of hypouricemia in severely disabled children. However, it was uncertain what factor of bedridden state influences the uric acid level in severely disabled children. Among many factors of a bedridden state that might influence the uric acid level, we examined the influence of elemental nutrition on the serum uric acid level in severely disabled children because many severely disabled children with marked hypouricemia receive elemental nutrition. Thirty-one severely disabled children were included in this study, who were divided into two groups—group A: 11 patients with elemental nutrition; group B: 20 patients with non-elemental nutrition. The laboratory data in both groups were analyzed statistically, using the *t*-test. The uric acid level was significantly decreased in group A compared with group B ($p < 0.01$) without elevation of urinary excretion of uric acid. Other laboratory data, except phosphate and potassium, did not differ between the two groups significantly. An elemental diet may be one factor that decreases the uric acid level in severely disabled children.

Keywords: Hypouricemia; Severely disabled children; Elemental diet; Enteral nutrition

1. Introduction

Severely disabled children receiving enteral nutrition for a long time suffer from various complications because of the severity of the underlying disorder needing the enteral nutrition and the enteral nutrition itself [1,2]. In a previous paper [3], we reported that the uric acid level was significantly decreased in non-ambulatory, severely disabled children treated with valproic acid (VPA). Both VPA and the non-ambulatory state decreased the uric acid level, statistically. VPA may cause renal tubular dysfunction, however, it remains unknown what factor in severely disabled children caused the hypouricemia in the previous study.

Regarding the etiology of hypouricemia in severely disabled children, apart from the effect of VPA, many factors of a bedridden state, such as nutrition (components of an enteral diet, calories, and elemental diet), hypoactivity, malabsorption, and other complications are suspected to influence the uric acid level. In this study, we examined the influence of elemental nutrition on the serum uric acid level in severely disabled children because many severely disabled children with marked hypouricemia receive elemental nutrition [4].

2. Patients and methods

2.1. Patients

Thirty-one severely disabled children were included in this study, and were followed in the outpatient clinic for pediatric neurology of Niigata City General Hospital from January 2001 to May 2002. To eliminate the possibility of a confounding effect of VPA, all the patients included in this study were given VPA for at least 6 months.

Twenty-four of these 31 patients were in group A (non-ambulatory patients taking VPA) in the previous study [3] and another seven patients being added in this study. Eighteen were boys and 13 were girls. They were 1–19 years of age. Twenty-two of these children had

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0387-7604/03/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0387-7604(03)00094-9

cerebral palsy and mental retardation as sequelae of perinatal brain insults, two sequelae of acute encephalitis, two sequelae of anoxic encephalopathy, one Sotos syndrome, one Cornelia de Lange syndrome, one 22q.11.2 deletion syndrome, one linear nevus sebaceus syndrome, and one Rett syndrome. There were no signs of inborn errors of metabolism, syndrome of inappropriate secretion of anti-diuretic hormone, or malnutrition in our patients.

The patients were divided into two groups according to whether they received elemental enteral nutrition. Group A: 11 patients receiving elemental enteral nutrition; group B: 20 patients receiving non-elemental nutrition. In group A, nine patients had Elental® containing 4.7 g protein/100 kcal, and two had Elental P® containing 3.1 g protein/100 kcal for at least 1 year. In group B, 10 patients ate usual diet and nine had Ensure liquid® containing 3.52 g protein/100 kcal, and one Racol® containing 4.38 g protein/100 kcal. All patients had various types of epilepsy and were treated with VPA. VPA was administered either alone (seven patients) or in combination with other antiepileptic drugs (24 patients): 12 clonazepam, two diazepam, two nitrazepam, three clobazam, three zonisamide, two clorazepate, three phenytoin, and three carbamazepine. The average dosages of VPA in groups A and B were 27.8 ± 6.4 mg/kg/day and 23.9 ± 13.0 mg/kg/day, respectively, which were not significantly different.

2.2. Method

Laboratory data including serum sodium, potassium, phosphate, uric acid, creatinine, total protein, hemoglobin, and urine pH, sodium, phosphate, uric acid, creatinine, and β2-microglobulin obtained routinely in outpatient clinic were used. To assess the renal tubular function in all groups, we measured the fractional excretion of uric acid (FEUA), fractional excretion of sodium (FENa), percent tubular reabsorption of phosphate (%TRP), and urinary excretion of β2-microbulin. FENa and FEUA were calculated using the formula: $FE_x = (U_x \times P_{cr}/P_x \times U_{cr}) \times 100$. The tubular reabsorption rate for phosphate was calculated with the formula: TRP = 1 − FE phosphate.

2.3. Data analysis

For comparison of the laboratory data between the patients in groups A and B, statistical analysis was performed using Student's *t*-test. The $p < 0.05$ was considered significant. Calculations were performed using the statistical software package StatView 5.0 (SAS Institute Inc., Cary, NC). All results are presented as means ± standard deviation.

3. Results

(Table 1) Patients in the two groups were similar in average age and sex. The uric acid level was significantly decreased in group A compared with group B ($p < 0.01$) (Fig. 1). The inorganic phosphate and potassium levels were significantly decreased in group A compared with group B ($p < 0.05$). A significant difference in FEUA was not recognized between groups A and B. No statistically significant differences were found between the two groups with respect to other parameters, such as serum sodium and creatinine, urinary pH, urinary β2-microglobulin, %TRP, and FENa. Nutritional factors, such as total protein, hemoglobin, and calories, were not significantly different between the two groups. Other adverse effects of VPA, such as liver dysfunction, hematologic abnormalities, and weight gain were not recognized in any patients.

4. Discussion

The results suggested that hypouricemia was more common in severely disabled patients receiving elemental nutrition compared with ones receiving a non-elemental diet. However, it is still unknown whether a component of the elemental diet itself or a secondary change of the gastrointestinal tract influences the uric acid level, or whether the pathological condition needing the elemental nutrition has something to do with hypouricemia. Although the phosphate and potassium levels were also decreased in group A, the reason is unclear. This might be a reflection of subclinical renal tubular dysfunction caused by VPA [3].

An elemental diet contains no purine. A long-term effect of purine-free nutrition on protein and uric acid homeostasis is not well recognized. It is known that hypouricemia is commonly recognized in patients receiving total parenteral nutrition in purine-free regimens [5–7]. However, purine deprivation evidently leads to an increase in de novo synthesis and the uric acid level is maintained within the normal range [8]. Several authors [5–7] have reported that a decreased plasma uric acid level is due to enhanced FEUA

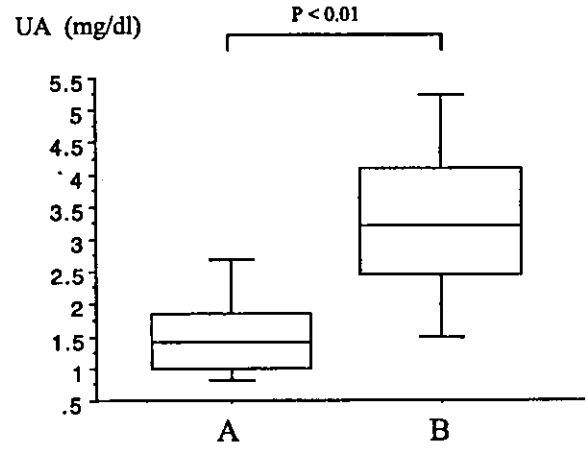

Fig. 1. Box and whisper plots of the serum uric acid levels in groups A and B. Upper line indicates 90 percentile and lower line indicates 10 percentile. UA, uric acid.

Table 1
Laboratory data in groups A and B

	Elemental ($n = 11$)	Non-elemental ($n = 20$)	Normal range	p
Age (years)	6.89 ± 6.17	4.90 ± 3.40		
Sex (M/F)	6/5	12/8		
UA (mg/dl)	1.53 ± 0.81	3.31 ± 1.37	2.5–5.8	<0.01
IP (mg/dl)	2.94 ± 1.41	4.49 ± 1.18	2.4–4.5	<0.05
K (mEq/l)	3.57 ± 0.96	4.16 ± 0.43	3.5–4.8	<0.05
Na (mEq/l)	139.5 ± 2.58	140.3 ± 2.94	140–146	n.s.
Cre (mg/dl)	0.35 ± 0.12	0.32 ± 0.10	0.4–0.8	n.s.
FEUA (%)	32.70 ± 28.65	17.41 ± 24.00	4–14	n.s.
% TRP (%)	87.73 ± 13.29	86.27 ± 20.96	60–90	n.s.
FENa	0.915 ± 1.202	0.644 ± 0.555	<1.0	n.s.
Urine pH	7.364 ± 0.67	7.39 ± 0.65	5.5–7.0	n.s.
β2 MG (mg/l)	22.23 ± 29.31	11.03 ± 29.20	<0.27	n.s.
TP (g/dl)	6.67 ± 0.60	6.54 ± 0.70	6.6–8.0	n.s.
Hb (g/dl)	12.52 ± 1.70	12.44 ± 1.15	10.9–14.3	n.s.
Cal (kcal/kg/day)	52.72 ± 12.19	59.58 ± 16.74		n.s.
Protein intake (g/kg/day)	2.32 ± 0.42			

Each value is expressed as mean ± SD. M, male; F, female; UA, uric acid; IP, inorganic phosphate; Cre, creatinine; FEUA, fractional excretion of uric acid; FENa, fractional excretion of sodium; %TRP, percent tubular reabsorption of phosphate; β2-MG, β2-microglobulin; TP, total protein; Hb, hemoglobin; Cal, calorie.

throughout total parenteral nutrition. The amino acids for parenteral nutrition are associated with the renal tubular reabsorption of uric acid. However, it is unclear whether the mechanism of hypouricemia is the same between parenteral nutrition and elemental enteronutrition. The deficiency of molybdenum (required as cofactor for uric acid synthesis) was reported extremely rarely as a cause of hypouricemia, during total parenteral nutrition [9]. Although we had not measured the serum level of molybdenum, we should also examine the molybdenum level when we see the hypouricemic patients.

An elemental enteral diet was known to influence pancreatic secretion [10], intestinal mucosal atrophy [11], bacterial translocation [12], and changes in the gastrointestinal microflora [13,14] like parenteral nutrition. The mechanism underlying this gastrointestinal influence of an elemental diet remains unclear. Janne et al. [11] reported colonic mucosal atrophy induced by an elemental diet in rats. Both mitotic and DNA synthetic activities decreased in the colonic mucosa during administration of the elemental diet. So, they concluded that atrophy of the colonic mucosa was probably mediated by a reduction in the proliferative activity of the stem cells in the mucosal glands. Another cause of intestinal villus atrophy with an elemental diet might be a lack of dietary fiber [15,16]. Chun et al. [15] reported that pectin feeding results in hyperplasia of the small intestinal mucosa and significant increases in the enzyme activities of the brush border membrane of the ileum. Soluble dietary fiber, such as pectin, added to an enteral diet has an effect on the proliferative activity of the colonic mucosa and improves the intestinal mucosal impairment. Although almost all reports concerning villus atrophy due to an elemental diet were based on animal experiments, Hosoda et al. [17] reported that intestinal mucosal atrophy was caused by an elemental diet in humans. The use of a pectin-supplemented enteral diet is recommended in severely disabled children to avoid intestinal atrophy.

The pathological findings for the gastrointestinal tract of severely disabled children after a long-term elemental diet were not known. However, Iai and Yamada [2] reported intestinal mucosal atrophy in an elderly severely disabled person after 25 years of enteral nutrition. This finding supports the fact that intestinal atrophy occurs in severely disabled children after prolonged elemental nutrition. Although there were no significant differences in calories, total protein, and hemoglobin between the two groups, and apparent malnutrition was not present in these two groups, some absorption disturbance of nutrition and subclinical malnutrition due to intestinal mucosal atrophy were suspected to cause hypouricemia.

To eliminate the influence of VPA [3], we included patients who were taking VPA in this study. It is ideal to select severely disabled children who have not taken VPA at all to compare the uric acid levels between two groups. However, we had such a small number of severely disabled children receiving elemental diet who had not taken VPA, that we had to include patients taking VPA to equal the condition of the patients.

In conclusion, although the exact mechanism remains obscure, prolonged elemental enteral nutrition might be a cause of hypouricemia in severely disabled children. The components of an elemental diet, secondary intestinal villus atrophy, changes in the microflora, and the underlying condition needing the elemental diet were suspected to have some relationship with hypouricemia in severely disabled

children receiving elemental nutrition. However, we will need to clarify the weight of these multi-factors by further investigations.

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Pediatrics International (2004) 46, 31–32

Original Article

Febrile convulsion during the acute phase of Kawasaki disease

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Abstract

Background: Although seizures occur in association with meningitis or encephalitis in Kawasaki disease, febrile convulsions in Kawasaki disease are considered to be extremely rare. The aim of the present study is to elucidate the incidence of febrile convulsion in the acute phase of Kawasaki disease, in Niigata City General Hospital, Niigata, Japan.

Methods: The study included 177 patients with Kawasaki disease. Patients ranged in age from 2 months to 10 years (mean age 26.89 ± 22.44 months). The study included 105 males and 72 females. The clinical records of Kawasaki disease patients were examined retrospectively.

Results: Febrile convulsions were not recognized in these 177 patients throughout the course of the disease, despite the presence of a high grade fever and their young age. However, eight of the 177 patients had experienced simple febrile convulsions during other febrile illness except for those with Kawasaki disease. In the acute phase of Kawasaki disease, only two patients showed generalized convulsion associated with prolonged consciousness disturbance and pleocytosis in the cerebrospinal fluid.

Conclusion: The incidence of febrile convulsions in the acute phase of Kawasaki disease might be extremely low, confirming the results of previous reports. Kawasaki disease is characterized by systemic vasculitis and is sometimes complicated by intracranial vasculitis. The incidence of electroencephalographic abnormalities and pleocytosis in the cerebrospinal fluid is higher in patients with Kawasaki disease. However, the reason why febrile convulsions did not occur in the acute phase of Kawasaki disease remains unknown, despite the presence of central nervous system involvement.

Key words febrile convulsion, Kawasaki disease.

Kawasaki disease is an acute febrile disorder of unknown etiology. Central nervous system complications in Kawasaki disease are uncommon: however, aseptic meningitis, encephalitis, cerebral infarction, subdural effusion, ataxia, facial nerve palsy and seizures have been rarely reported in children with this disease. Although the etiology of the central nervous system involvement remains obscure, systemic vasculitis, including the central nervous system, might play a role. According to previous reports of Kawasaki disease,[1–8] seizures occur in association with meningitis or encephalitis. Febrile seizures in Kawasaki disease are considered to be extremely rare. When febrile seizures occur, they usually affect patients under 5 years of age, and are accompanied by a high grade fever. Thus, to elucidate the incidence of febrile convulsion in the acute phase of Kawasaki disease, we retrospectively examined the clinical records of Kawasaki disease patients admitted to Niigata City General Hospital, Niigata, Japan.

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Received 22 May 2003; revised 30 July 2003; accepted 11 August 2003.

Methods

The study included 177 patients admitted to Department of Pediatrics, Niigata City General Hospital, between January 1991 to April 2002, for the treatment of Kawasaki disease. The patients ranged in age from 2 months to 10 years (mean age 26.89 ± 22.44 months). The study included 105 males and 72 females.

Results

Febrile convulsions were not recognized in our 177 patients throughout the course of the disease, despite the presence of a high grade fever and their young age. However, eight of the 177 patients had experienced simple febrile convulsions during febrile illness except for those with Kawasaki disease. In the acute phase of Kawasaki disease, only two patients showed generalized convulsion associated with prolonged consciousness disturbance and pleocytosis in the cerebrospinal fluid. A 2-month-old boy developed generalized tonic convulsions lasting 15 min following prolonged unconsciousness.

The cerebrospinal fluid examination revealed a total cell count of 85/μL, and protein at 42 mg/dL. His serum sodium concentration was 117 mEq/L. Another 2-month-old boy developed prolonged generalized tonic convulsions and was on mechanical ventilation. His cerebrospinal fluid had a total cell count of 27/μL, with protein at 45 mg/dL. His serum sodium concentration was 122 mEq/L. Thirteen days of consciousness disturbance followed initiation of neurological symptoms.[9] Two patients recovered completely without any neurological sequelae.

Table 1 Incidence of febrile convulsion in Kawasaki disease in previously reported cases

Study	Incidence of FC	Other CNS complications
Otsuka *et al.*[1]	1/155 (0.64%)	Meningitis 6/155
Asou *et al.*[2]	8/498 (1.6%)	Four CNS involvements
Kajitani *et al.*[3]	1/402 (0.24%)	One MCLS/FC197
Nanbo *et al.*[4]	0/152 (0%)	Six FC after MCLS
Terasawa *et al.*[5]	0/540 (0%)	Six CNS involvements
Present study	0/177 (0%)	Two seizures with other etiology

FC, febrile convulsion; CNS, central nervous system; MCLS, mucocutaneous lymph node syndrome.

Discussion

In previous reports of seizures associated with Kawasaki disease (Table 1), the incidence of febrile convulsions was reported to be 1/155,[1] 8/498,[2] 1/402,[3] 0/152[4] and 0/540,[5] retrospectively. Nanbo *et al.* also reported that febrile convulsions did not occur in 152 Kawasaki disease patients, however, febrile convulsions associated with other febrile illness occurred almost at the same rate as in other children.[4] Yokoyama *et al.* reported that febrile convulsions were recognized in one of 26 patients with Kawasaki disease who were examined by electroencephalography.[6] Mitsudome *et al.* also reported that febrile convulsions occurred in four of 62 patients with Kawaski disease, who were examined by electroencephalography.[7] In these two reports,[6,7] bias was present in that the electroencephalography examination was performed with the suspicion of central nervous system involvement. Thus, the incidence of febrile convulsion might be higher in these two reports than in other reports. Otaki *et al.* reported that patients with Kawasaki disease developed seizures associated with hyponatremia, similar to our two cases.[8] Our two patients who developed seizures were both 2 months old and presented with hyponatremia and pleocytosis in the cerebrospinal fluid. They have never been diagnosed as having febrile convulsion, and their clinical courses resembled acute encephalitis or encephalopathy.

The incidence of febrile convulsion was reported to be 5–10%. Febrile convulsions ranged from 6 months to 4 years, being approximate to the ages of the patients with Kawasaki disease. Although this study was not a statistical analysis, the incidence of febrile convulsions in the acute phase of Kawasaki disease might be extremely low confirming the results of previous reports. Kawasaki disease is characterized by systemic vasculitis, mainly involving the coronary arteritis and sometimes complicated by intracranial vasculitis. On histopathological investigation, aseptic chorio and/or leptomeningitis, severe edema, necrosis, localized status spongiosus and vascular change such as endoarteritis, periarteritis and perivascular cuffing were present in some of their patients.[10] The incidence of electroencephalographic abnormalities and pleocytosis in the cerebrospinal fluid is higher in patients of Kawasaki disease. Such a pathologic mechanism could also affect the central nervous system and be responsible for the neurologic symptoms. However, the reason that febrile convulsions did not occur in the acute phase of Kawasaki disease remains unknown, despite the presence of central nervous system involvement. Its mechanism might be related to the etiology of Kawasaki disease. If the mechanism is determined, it will be useful for developing preventive methods for febrile convulsions. Further investigation is necessary to elucidate these matters.

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Clinically mild encephalitis/ encephalopathy with a reversible splenial lesion

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Abstract—*Objective:* To clarify whether patients with clinical diagnoses of encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum (SCC) share common clinical features. *Methods:* Possible encephalitis/encephalopathy patients with a reversible isolated SCC lesion on MRI were collected retrospectively. Their clinical, laboratory, and radiologic data were reviewed. *Results:* Fifteen encephalitis/encephalopathy patients with a reversible isolated SCC lesion were identified among 22 patients referred for this study. All 15 patients had relatively mild clinical courses. Twelve of the 15 patients had disorders of consciousness. Eight patients had seizures, and three of them received antiepileptic drugs. All 15 patients clinically recovered completely within 1 month (8 patients within a week) after the onset of neurologic symptoms. The SCC lesion was ovoid in six patients; it extended irregularly from the center to the lateral portion of SCC in the other eight patients. Homogeneously reduced diffusion was seen in all seven patients who underwent diffusion-weighted imaging. There was no enhancement in the five patients so examined. The SCC lesion had completely disappeared in all patients at follow-up MRI exams between 3 days and 2 months after the initial MRI (within 1 week in eight patients). *Conclusion:* The clinical features among the affected patients were nearly identical, consisting of relatively mild CNS manifestations and complete recovery within 1 month.

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MRI is accepted as a more sensitive technique than CT for the diagnosis of encephalitis/encephalopathy and is particularly useful for detecting early changes in the brain. An MRI finding of an ovoid reversible lesion in the central portion of the splenium of the corpus callosum (SCC) without any accompanying lesions has been reported in around 20 patients with epilepsy receiving antiepileptic drugs.[1-5] The MR finding is unusual but has been reported in a few patients with encephalitis/encephalopathy caused by various agents such as influenza virus,[6] rotavirus,[7] and O-157 *Escherichia coli*.[8] These patients had no history of seizures or administration of antiepileptic drugs. These previously reported cases of encephalitis/encephalopathy were clinically mild, and the patients recovered completely. We retrospectively reviewed the clinical, radiologic, and laboratory findings of 15 Japanese patients with encephalitis/encephalopathy with a reversible isolated SCC lesion to clarify whether they share common clinical features and whether their MRI findings are identical to those reported in the literature secondary to epilepsy.[1-5]

Patients and methods. Possible encephalitis/encephalopathy patients with a reversible isolated lesion involving the central portion of the SCC on MRI were collected retrospectively by sending out a questionnaire to the members of the Annual Zao Conference on Pediatric Neurology and to some members of the Japanese Society of Pediatric Neurology and Japanese Society of Neuroradiology. We reviewed MR scans and charts of these patients, including information about symptoms, clinical diagnosis, medications, treatments, prognosis, results of CSF analysis, and EEG. The diagnosis of encephalitis has been defined as acute onset of brain dysfunction such as seizures and disorders of consciousness with inflammatory changes such as pleocytosis of CSF. When there was no evidence of inflammatory change, we used the term "encephalopathy." A reversible isolated SCC lesion was defined, for the purposes of this study, as a lesion involving the central portion of the SCC without any accompanying lesions on the initial MRI, which disappeared on the follow-up study.

Results. We identified 15 encephalitis/encephalopathy patients with a reversible isolated SCC lesion among the 22 patients whose clinical records and MRI examinations were referred for this study. Three patients were excluded because they had lesions in the white matter or cerebellum as well as in the SCC. Three were excluded because they had no follow-up MRI study. One patient, who was taking oral antiepileptic drugs, had another potential cause for the splenial lesions and was eliminated as well. The clini-

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Received February 19, 2004. Accepted in final form July 21, 2004.

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Table 1 Clinical data for encephalitis/encephalopathy with reversible central splenial lesion

Patient no.	Age/ sex	Pathogen	Initial symptom	Premedication	CNS manifestation (onset day)	CNS diagnosis	Therapy	Prognosis	CSF	EEG
1	3/F	Unknown	Diarrhea, vomiting	None	Seizure, motor deterioration (3)	Encephalitis	PB, Dex	CR (d 21)	CC, 34	Slow BA
2	2/M	Unknown	Fever	None	Seizure, drowsiness (3)	Encephalopathy	Diazepam	CR (d 6)	Normal	Slow BA
3	4/F	Unknown	Fever, diarrhea	None	Seizure, blindness (3)	Encephalopathy	Diazepam	CR (d 5)	NE	Slow BA
4	5/M	Influenza A	Fever	None	Seizure, delirium (2)	Encephalopathy		CR (d 3)	Normal	Slow BA
5	5/M	Adenovirus	Fever	Amantadine	Ataxia, drowsiness (3)	Encephalopathy	IVIGG	CR (1 mo)	Normal	Slow BA
6	7/M	Mumps	Fever, parotitis	None	Delirium (3)	Meningoencephalitis	IVIGG	CR (d 5)	Pleocytosis	Slow BA
7	59/F	Unknown	Fever	None	Vertigo (1), lethargy (2)	Encephalitis	ACV, antibiotics	CR (d 8)	CC, 500	Slow BA
8	18/F	Unknown	Fever	None	Seizure, delirium (2)	Encephalitis	PB, PSL	CR (1 mo)	CC, 17	Slow BA and spikes
9	19/M	Unknown	Fever, cough	None	Delirium (7), seizure (8)	Encephalitis	ACV, PHT, PSL	CR (d 17)	Normal	Slow BA
10	8/M	Mumps	Fever, vomiting	None	Headache (1), seizure, delirium (4)	Meningoencephalitis		CR (d 10)	CC, 119	Normal
11	4/F	Unknown	Fever	None	Seizure, delirium (2)	Encephalopathy	Antibiotics, diazepam	CR (d 5)	Normal	NE
12	25/F	VZV	Fever, vesicula	None	Headache, drowsiness, nausea (3)	Encephalopathy	ACV	CR (d 10)	NE	NE
13	9/F	Unknown	Fever	None	Neck stiffness (3), vertigo, tremor (7)	Meningoencephalitis	ACV, antibiotics, Dex	CR (d 21)	CC, 337	Slow BA
14	22/M	Unknown	Fever	None	Hallucination, delirium (6)	Encephalopathy	ACV, antibiotics, PSL	CR (d 11)	Normal	Slow BA
15	10/M	Unknown	Fever	None	Drowsiness (3)	Encephalopathy, rhabdomyolysis	Antibiotics, IVIGG	CR (d 14)	Normal	Slow BA

PB = phenobarbital; Dex = dexamethasone; CR = complete recovery; CC = cell count (/mm^3); BA = basic activity; NE = not examined; IVIGG = IV immunoglobulin G; ACV = acyclovir; PSL = prednisolone; PHT = phenytoin; VZV = varicella zoster virus.

cal records and radiologic examinations of the remaining 15 patients were reviewed by the authors and are the basis of this study. The findings of the 15 patients are summarized in tables 1 and 2.

The 15 patients (8 male and 7 female; age 2 to 59 years) developed normally until the onset of neurologic symptoms. Fever preceded neurologic symptoms in all 15 patients. Directly causative agents were identified by rapid antigen-detection assay, PCR, positive IgM, or longitudinally increased IgG in 5 of 15 patients. The pathogens included influenza A, mumps virus (two patients), varicella-zoster virus, and adenovirus. The onset of neurologic symptoms ranged from day 1 to 7 of the illness. Eight of the 15 patients had seizures. Other neurologic symptoms included disorders of consciousness (12 patients), vertigo (2 patients), motor deterioration, blindness, ataxia, tremor, and hallucinations. No patient needed mechanical ventilation. Three patients had received antiepileptic drugs (phenobarbital for two patients and phenytoin for another) at the time of MR studies. Analysis of CSF revealed pleocytosis in 6 of 13 examined patients but normal glucose and protein levels. EEG showed slow basic activity characteristic of encephalitis/encephalopathy in 12 of 13 examined patients. Though their treatments were variable (e.g., corticosteroids for five patients and IV IgG administration for three patients), all 15 patients clinically recovered completely within 1 month (8 patients within 1 week after the onset of neurologic symptoms) without sequel.

In 14 of the 15 patients, the initial MR study was performed within 4 days of the onset of neurologic symptoms. On axial images, the lesion was ovoid and in the center of the SCC in six patients (Patients 3, 4, 7, 8, 13, 14) (figure 1) and extended irregularly into the lateral portion of SCC in the other eight patients (figure 2). In Patient 12, a lesion in the central portion of the SCC was detected on sagittal T1- and T2-weighted images (axial T2-weighted image being unavailable). There was no obvious correlation between the shape of SCC lesion and the scan date, neurologic symptoms (presence or absence of seizures, date of complete recovery), or laboratory findings. The SCC lesion was, compared with the surrounding splenium, homogeneously hyperintense on T2-weighted images and isointense to slightly hypointense on T1-weighted images. Homogeneously reduced diffusion (hyperintensity on diffusion-weighted images and low apparent diffusion coefficient [ADC] values) was seen in all seven patients examined by diffusion-weighted imaging. There was no enhancement of the SCC lesion after gadolinium adminis-