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Brain & Development 24 (2002) 710–714

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Original article

Abnormal white matter lesions with sensorineural hearing loss caused by congenital cytomegalovirus infection: retrospective diagnosis by PCR using Guthrie cards

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Received 25 February 2002; received in revised form 13 May 2002; accepted 24 May 2002

Abstract

We report on two patients with congenital cytomegalovirus (CMV) infection asymptomatic at birth that was diagnosed retrospectively by polymerase chain reaction (PCR) of CMV DNA using blood stored on Guthrie cards. Neuroimaging studies showed abnormal myelination without any gray matter abnormalities. In the differential diagnosis of patients with abnormal white matter lesions and sensorineural hearing loss, one should consider congenital CMV infection. When investigating the etiology of patients with behavioral problems, migrational disorder, or white matter disease, PCR analysis of CMV DNA using blood stored on Guthrie cards might be helpful.

Keywords: Cytomegalovirus; Congenital infection; Polymerase chain reaction; Dysmyelination; Newborn mass screening

1. Introduction

Cytomegalovirus (CMV) is the most common cause of congenital and perinatal viral infections worldwide. Congenital infection occurs in 1% of all live births in developed countries and in an even higher percentage in developing nations [1]. Only 10% of infected infants have symptoms at birth. The manifestations of congenital infection seen most frequently at birth are petechiae, hepatosplenomegaly, jaundice, and microcephaly. Intrauterine growth retardation, cerebral calcifications, prematurity, inguinal hernia and chorioretinitis are less common [2]. In contrast, 90% of infected infants are asymptomatic at birth, although about 15% of these infants suffer from hearing loss [2]. Although neuroimaging studies of patients with symptomatic congenital CMV infection have been reported [3–7], there are few reports on patients with congenital CMV infection asymptomatic at birth [8,9]. Recently, the retrospective diagnosis of congenital CMV infection has become possible using polymerase chain reaction (PCR) of CMV DNA in blood stored on Guthrie cards [9,10]. Here, we report on two children who were asymptomatic at birth, but who had abnormal white matter lesions detected by magnetic resonance imaging (MRI), with sensorineural hearing loss, and were diagnosed as congenital CMV infection by PCR of CMV DNA in blood stored on Guthrie cards.

2. Case reports

2.1. Case 1

A 9-year-old girl had a birth history of normal gestation by vacuum delivery from healthy, non-consanguineous parents. Her birth weight was 2432 g, which is less for a term baby. She did not have birth asphyxia. Her early development was normal (head control: 4 m, sit alone: 8 m, walk alone: 12 m). However, she visited our hospital at the age of 16 months because her father noticed that she had difficulty in hearing. A computed tomographic (CT) scan of the head taken at that time showed multiple areas with low density in the cerebral white matter, but did not show calcification of the cerebral parenchyma.

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PII: S0387-7604(02)00088-8

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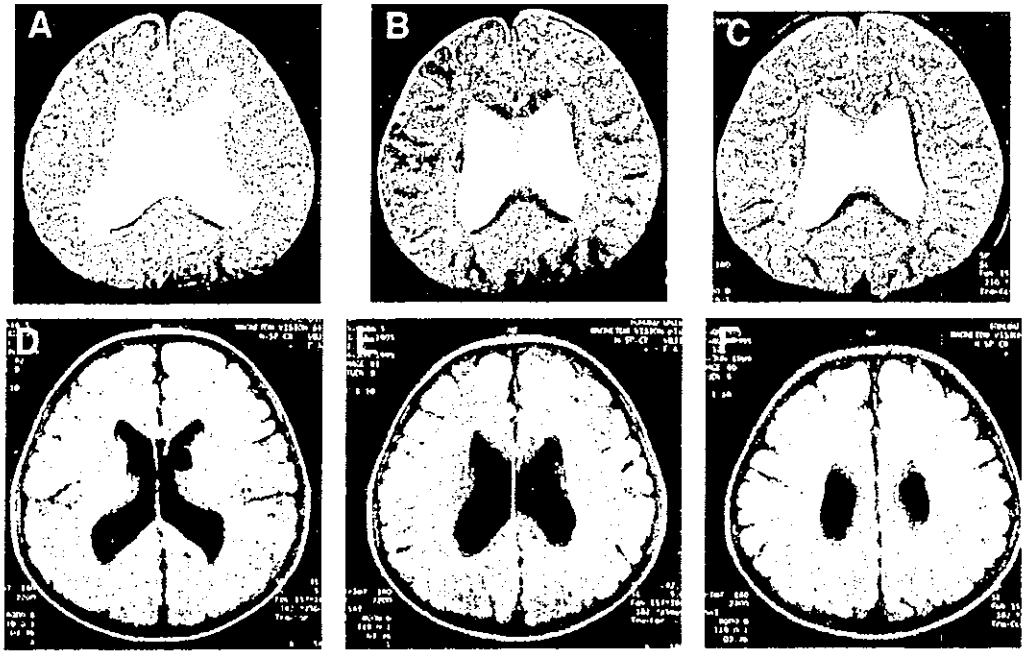

Fig. 2. MRI (T_2-weighted: (A– C) and FLAIR: (D–F) images) of Case 2. (A): 9 months; (B): 19 months; and (C–F); 46 months.

20 months of age and 3 years of age revealed multiple high-intensity lesions on T_1-weighted and fluid attenuated inversion recovery (FLAIR) images, which were distributed throughout the white matter, as in the initial study (Fig. 2). Proton (^{1}H) magnetic resonance imaging (MRS) showed no substantial difference in the *N*-acetylaspartate (NAA)/phosphocreatine and creatine (Cre) ratio or choline-containing compound (Cho)/Cre ratio between the normal and abnormal white matter regions (Fig. 3). In spite of normal left ear function, her DQ at 33 months of age was 42. Gross motor function and word expression were especially delayed. Her serum CMV IgG titer was high (1:2816) at the age of 3 years. After receiving informed consent, PCR clearly amplified CMV DNA from blood stored on Guthrie cards that was performed after receiving informed consent. The patient showed some minor anomalies and IUGR at birth. In the literature, it is not clear how many symptoms are required to categorize newborns as having symptomatic congenital CMV infection. Some reports do not categorize infants who show only IUGR at birth as symptomatic, unless at least one other abnormality is also present [12]. We adopted this criterion when considering this patient. Therefore, this patient was not categorized as having symptomatic congenital CMV infection. The minor anomalies were likely to be coincidental.

3. Discussion

Neuroimaging studies of patients with symptomatic congenital CMV infection have revealed multiple abnormalities, such as lissencephaly, pachygyria, micropolygyria, dysmyelination, paraventricular cysts, cerebellar hypoplasia, and intracranial calcification [3–7]. The heterogeneity of CNS abnormalities likely depends on the developmental stage at which the fetus is infected by CMV [5]. Infection before the 18th week of gestation leads to lissencephaly, while infection between the 18th and 24th week of gestation leads to focal dysplastic cortices [5]. The existence of brain CT scan abnormalities in neonates – including intracerebral calcification, ventricular dilatation, white matter abnormalities, cortical atrophy, and migrational disorder – is well correlated with developmental outcomes in symptomatic congenital CMV infection [6]. In contrast, there are few neuroimaging studies of patients with congenital CMV infection asymptomatic at birth [8,9] because classic serological and virological tests cannot distinguish whether an infection was congenital or of later occurrence. Williamson et al. reported that CT scans revealed periventricular radiolucency in 23% of 56 patients with congenital CMV infection asymptomatic at birth and intracranial calcification in 5% of these subjects [8]. Recently, Malm et al. reported a patient with pachygyria who was asymptomatic at birth, but had positive PCR amplification of CMV DNA retrieved from a stored Guthrie card [9].

In our patients, white matter abnormalities were the main abnormal findings that showed CNS disturbance. Similar white matter abnormalities have been reported in patients with symptomatic congenital CMV infection associated with or without migrational anomalies [3–5]. White matter problems without migrational abnormalities seem to indicate infection after the 26th–28th week of gestation, since neuronal growth and migration are completed at around 26

infection asymptomatic at birth in our patients, as in a previous report [9]. CMV DNA in blood stored on Guthrie cards was evident in 80% of children with confirmed congenital CMV infection [10]. Previous studies of school-aged children revealed that congenital CMV infection asymptomatic at birth, in the absence of hearing loss, is not associated with increased risk of intellectual or learning deficits [14]. However, behavioral problems such as hyperactivity, autism, and conduct disorder are still a matter of concern in patients with congenital CMV infection asymptomatic at birth [13,15]. In investigating the etiology of patients with behavioral problems, migrational disorders, and white matter disease, PCR analysis of CMV DNA using blood stored on Guthrie cards might be helpful.

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Brain & Development 24 (2002) 194–196

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

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Case report

Two successful cases of bromide therapy for refractory symptomatic localization-related epilepsy

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Received 30 November 2000; received in revised form 16 January 2002; accepted 18 January 2002

Abstract

Potassium bromide was tried for two children with daily convulsive focal motor seizures with unconsciousness and focal motor seizure status. The treatment resulted in complete cessation of the attacks.

It has been reported that bromide is effective for generalized tonic–clonic seizures and not for complex partial seizures, such as convulsive focal motor seizures with unconsciousness. However, our experiences provide evidence that bromide is one of the useful therapeutic agents for intractable symptomatic localization-related epilepsy. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Symptomatic localization-related epilepsy; Potassium bromide; Intractable partial seizures

1. Introduction

For half a century until the introduction of phenobarbital (PB) in 1912, bromide (BR) had been the principal anticonvulsant [1]. However, it fell into disuse when new antiepileptic substances were discovered. It has been reported that the antiepileptic spectrum of BR is usually limited to tonic–clonic seizures; but the efficacy of BR in focal seizures has not yet been examined thoroughly.

Two interesting cases of symptomatic localization-related epilepsy are presented below: the patients were treated with BR, which produced a positive response to refractory convulsive focal motor seizures with unconsciousness and inhibited their secondary generalization.

2. Case report

2.1. Case 1

The patient, a 15-month-old female, suffered from developmental retardation as the sequelae of severe neonatal asphyxia. Magnetic resonance imaging (MRI) of her brain showed severe cerebral atrophy and multicystic encephalomalacia. Focal clonic seizures of the left upper limb and face with disturbance of consciousness, occasionally secondarily generalized, have been noted since the age of 5 months. Ictal electroencephalogram (EEG) showed localized spikes over the right anterior region (Fig. 1). Interictal EEG showed multifocal spike foci. The seizures became more frequent and at the age of 7 months, the incidence exceeded 50 or 60 a day. When she was admitted to our hospital at the age of 8 months, her consciousness and respiration were affected due to the frequently recurrent seizures.

Peripheral blood analyses and chemical examinations revealed no clear-cut abnormalities. No findings suggestive of congenital anomalies were noted. A number of optimal-dose oral anticonvulsant monotherapies and polytherapies were attempted to no avail.

At the age of 15 months, oral potassium bromide (KBr), at a maximum dose of 80 mg/kg/day, was added to the ongoing therapeutic regimen with informed consent, which brought the seizures under complete control within 1 month (Fig. 2). The blood concentration of BR was 240 mg/dl. The seizures remained completely free for 4 months. There were no serious side effects except for spurious hyperchloremia and mild somnolence.

2.2. Case 2

The patient, an 8-year-old male, had been followed up because of psychomotor retardation of unknown origin since the age of 2 months. His visual and auditory acuities

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PII: S0387-7604(02)00023-2

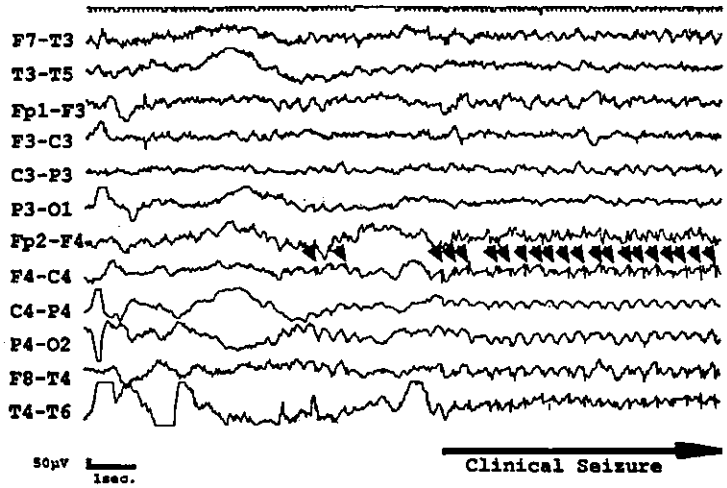

Fig. 1. Ictal EEG of the first case before treatment with KBr demonstrates rhythmic localized spike activity over the right anterior region (arrow), when the patient developed clonic convulsions of the left upper limb.

were disturbed, and multiple minor anomalies were observed. At the age of 4 months, audiogenic myoclonic seizures developed, and these changed to right or left hemiconvulsions frequently associated with secondary generalization since the age of 16 months. In spite of various oral anticonvulsants, seizures appeared daily and the patient sometimes fell into status convulsivus. At the age of 3 years, the brain MRI revealed a large arachnoid cyst in the right middle temporal fossa with mild brain atrophy especially in the bilateral frontal lobes. The interictal EEG showed multifocal spikes in bilateral occipital areas. At the age of 8 years and 2 months, he was admitted to our hospital because of status convulsivus that consisted of repetitive right or left hemiconvulsions with secondary generalization. The ictal EEG revealed polyspike bursts appearing in the left or right parietal to occipital areas, showing a migration to the other side of the same areas during seizures. The ictal SPECT, while he had a clonic convulsion of the left extremities, revealed hyperperfusion of the right upper temporal, parietal and occipital cortices. The seizures were finally controlled by high dose continuous intravenous injection of thiopental under respirator care. However, the seizures reappeared when the dose of thiopental was gradually decreased. The seizures were not controlled in spite of the administration of various other anticonvulsants. Therefore, the patient began to receive KBr monotherapy at a dose of 86 mg/kg/day with informed

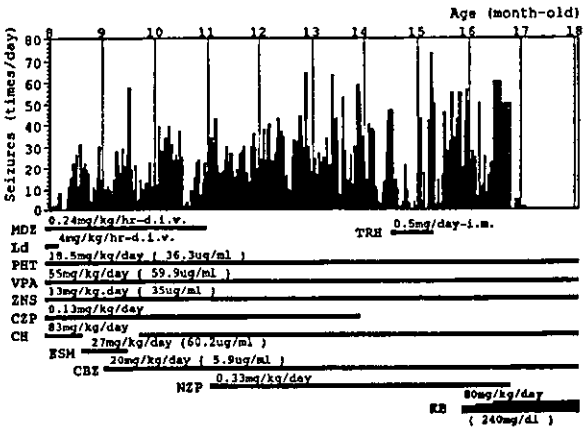

Fig. 2. Clinical course of the first case. At the age of 15 months, oral KBr was added to the ongoing therapeutic regimen, which brought the seizures under complete control within 1 month. Numbers above the horizontal bars indicate the maximum dosage of each drug, and numbers in parentheses indicate the maximum blood concentration of each drug. CBZ, carbamazepine; CH, chloral hydrate; CZP, clonazepam; ESM, ethosuximide; KBr, potassium bromide; Ld, lidocaine; MDZ, midazolam; NZP, nitrazepam; PHT, phenytoin; TRH, thyrotropin-releasing hormone; VPA, valproate; and ZNS, zonisamide.

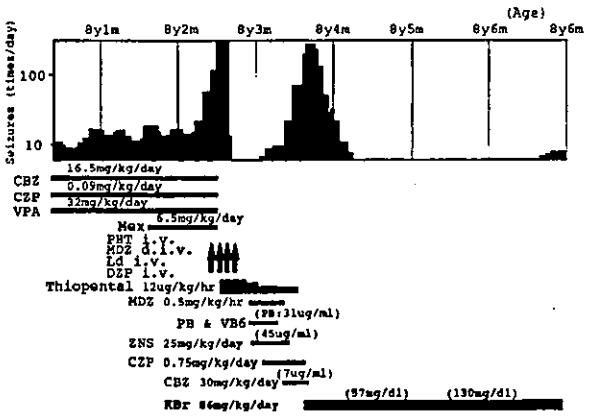

Fig. 3. Clinical course of the second case. At the age of 8 years, the patient began to receive KBr. The seizures completely ceased on the 18th day of administration. Numbers above the horizontal bars indicate the maximum dosage of each drug, and numbers in parentheses indicate the maximum blood concentration of each drug. DZP, diazepam; Mex, mexiletine; PB, phenobarbital; and VB6, vitamin B6.

consent. The seizures became less frequent and less intensive 4 days after administration, and completely ceased on the 18th day of administration (Fig. 3). The blood concentrations of BR on the 5th and 16th day were 57 and 130 mg/dl, respectively. The patient remained completely free of seizures for 2.5 months. There were no serious side effects except for spurious hyperchloremia.

3. Discussion

The reasons why BR has fallen into disuse can be explained as follows: first, the biological half-life of BR ions in human blood is 12–14 days, and 40–50 days are required to reach a steady state [2], so it is difficult to refer to blood concentration and determine the dosage or conduct so-called therapeutic drug monitoring. Secondly, the therapeutic serum level of this drug is considered to approximate the toxic level. In addition, various side effects (such as drowsiness, anorexia, and skin rash) are known. Ryan and Baumann reported in their review [3] that the adverse effects of BR are significant and potentially life threatening, and that severe bromism is associated with BR concentration above 200 mg/dl and may manifest as restlessness, headache, delirium, and dementia, which may be accompanied by hallucinations. Therefore, monitoring of the patient's condition and serum BR levels is necessary to safely treat epilepsy. Another important clinical problem is induction of a true or spurious serum electrolyte imbalance. Through a large intake of sodium chloride, BR ions are displaced by chloride ions, resulting in a drop in the serum level of BR. When the intake of sodium chloride is reduced, the serum level of BR increases and toxic symptoms may develop [4]. On the other hand, laboratory examinations suggest the presence of spurious hyperchloremia, which may develop due to interference when the ion-selective electrode method is employed to measure the chloride ions while the serum BR level is high [5]. In our two cases, laboratory studies also showed spurious hyperchloremia (respectively, maximum, 143 and 129 mEq/l) and a change of the electrolyte-determining unit was required.

The pharmacological activity of BR is still considered to have been inadequately explored. The γ amino butyric acid-A (GABA-A) receptor, which is reputedly associated with anticonvulsive effects, appears to be coupled with a chloride channel and a benzodiazepine receptor [6]. BR is rapidly absorbed and distributed as BR ions: they partially displace chloride ions, become bound to the chloride channel, and exert an anticonvulsant effect through anion potentiation of the benzodiazepine receptors. However, detailed pharmacological mechanisms have not yet been elucidated.

In spite of these problems, positive results with BR treatment for refractory epilepsy have recently been reported. Oguni et al. [7] reported that eight of 22 (36%) infants with severe myoclonic epilepsy in infancy (SME) were treated with BR, which produced an excellent result within 3 months of BR introduction. Dreifuss and Bertram [2] concluded that those with therapy-resistant generalized tonic–clonic seizures (GTCS) responded well to BR therapy. Woody [8] concluded that a combined therapy of BR with valproate appeared to be particularly effective.

It has been reported that the antiepileptic spectrum of BRs commonly refers to GTCS and not to partial seizures [2]. However, more recently, Okuda et al. [9] reported that BR controlled migrating partial seizures in infancy. In our case 1, frequent convulsive focal motor seizures with unconsciousness and their frequent secondary generalization were completely stopped by add-on therapy with BR. We also successfully controlled status epilepticus of localization-related epilepsy in patient 2 with BR monotherapy. We selected BRs as an add-on therapy and monotherapy for each patient by chance. However, these results showed that both styles of therapy were effective. Our experiences provided an evidence that BR is one of the useful therapeutic agents for symptomatic localization-related epilepsy with refractory seizures. The reason why the seizures of the two cases recurred after 4 months and 2.5 months, respectively, is unclear. Some form of drug tolerance mechanism might occur. However, after the recurrence, uncontrollable frequent seizures like before did not cause further problems. A more extensive scale study will be needed to confirm the efficacy of BR in treating localization-related epilepsy.

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Mutation in the caveolin-3 gene causes a peculiar form of distal myopathy

Abstract—The authors describe a patient with sporadic distal myopathy associated with reduced caveolin-3 in muscle fibers in which the muscle atrophy was restricted to the small muscles of the hands and feet. Gene analysis disclosed a heterozygous 80 G→A substitution in the caveolin-3 gene that was identical to that of reported cases of elevated serum creatine kinase. This patient further demonstrated possible clinical heterogeneity of myopathies with mutations in the caveolin-3 gene.

NEUROLOGY 2002;58:323–325

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Caveolin-3 is the muscle-specific protein product of the caveolin gene family and a principal integral membrane component of caveolae.[1] Caveolin may function as a scaffolding protein for organizing and concentrating caveolin-interacting molecules and may play a pivotal role in essential cellular functions such as signal transduction and lipid metabolism.[2]

Recently, mutations in the human caveolin-3 gene have been shown to cause autosomal-dominant limb girdle muscular dystrophy.[3] Subsequently, other mutations in the caveolin-3 gene have been reported to be associated with sporadic cases in infants with elevated serum creatine kinase.[4,5] These findings imply that caveolin-3 gene mutations may cause various forms of myopathies.

We report a sporadic case of a patient with a peculiar form of distal myopathy in which the caveolin-3 gene mutation was identical to that in cases of infants with elevated serum creatine kinase, reported previously.[4]

Case report. The patient was first admitted to the pediatric division of our hospital at the age of 12 because of palpitation. Her serum creatine kinase concentration was 2,092 IU/L (normal, <135). Slight atrophy was suspected only in her hypothenar muscles. Needle electromyography showed myopathic changes restricted to the distal parts of the upper extremities such as the opponens pollicis. A biopsy specimen from the biceps brachii revealed mild myopathic changes. Although infrequent premature contractions were observed, cardiac functions were normal. She did not have difficulties in her daily life during junior high school or high school. When she was admitted to another hospital at age 25 because of gastritis, elevated serum creatine kinase was noticed again by a physician. She was then referred to our hospital. Her parents were unrelated, and the family history was negative for neuromuscular disorders. Serum levels of creatine kinase in her parents were normal.

On examination, her height was 170 cm and her weight was 70 kg. Her musculature was well developed and muscle atrophy was observed only in the small muscles of her hands and feet (figure 1). The muscle strength of the proximal limbs, forearms, and trunk were normal, except for mild weakness in neck flexion. She could stand on the tips of her toes and heels. The grasping power was 23 kg in the right hand and 26 kg in the left hand. In both hands, the muscle strength was moderately reduced in the palmar interossei and opponens pollicis muscles, and slightly reduced in the dorsal interossei muscles. Deep tendon reflexes were normally elicited. All sensory perceptions tests were normal. Her serum creatine kinase concentration was 2,154 IU/L, aspartate aminotransferase concentration was 57 IU/L (normal, <35), and lactase dehydrogenase activity was 816 IU/L (normal, <453). The serum level of total cholesterol was slightly elevated at 267 mg/dL (normal, <220 mg/dL). Chest roentgenogram and electrocardiogram showed no abnormalities.

Needle electromyography showed myopathic motor unit potentials of decreased duration and amplitude on volition in the first dorsal interossei, deltoid, and sternocleidomastoid muscles. No spontaneous activities were observed in any of the muscles examined. Motor and sensory nerve conduction studies were normal in both upper and lower limbs. The muscle biopsy specimen from the biceps brachii showed a mild variation in fiber size, increased centrally placed nuclei, and type 1 fiber predominance.

Methods. *Immunohistochemistry and Western blot analysis.* Frozen muscle sections were prepared from the patient and from normal control tissue. Antibodies used for immunohistochemistry included monoclonal antibodies against caveolin-3 (BD Transduction laboratories, Lexington, KY), dystrophin, β-dystroglycan, merosin, and polyclonal antibodies against α-sarcoglycan and dysferlin, which was described previously.[6] Western blot analysis was performed using the monoclonal antibody for caveolin-3 and the polyclonal antibody for dysferlin. The muscle samples were processed as described previously.[6]

Genetic analysis. Genomic DNA extracted from peripheral blood lymphocytes of the patient, after informed

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Supported by grants-in-aid from the Japan Foundation for Aging and Health, and the Ministry of Health, Labor and Welfare (M.A., I.N., Y.K.H., I.N., K.A.) and grants-in-aid for Scientific Research (B, 12557058) from the Japan Society for Promotion of Science (M.A., Y.I.).

Received July 6, 2001. Accepted in final form October 7, 2001.

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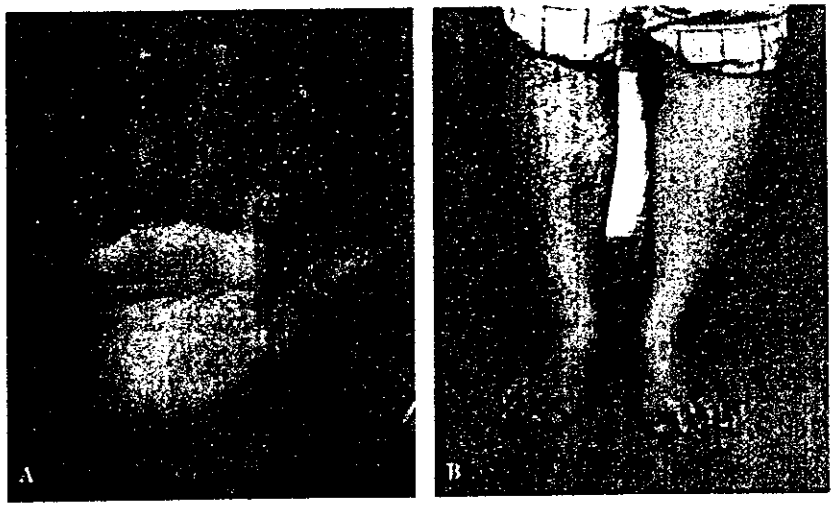

Figure 1. (A) The right hand of the patient shows muscle atrophy in the thenar and hypothenar muscles. (B) The feet of the patient show muscle atrophy on both sides of each foot. In contrast, the calf muscles and anterior tibial muscles are well developed.

consent, was used as a template for PCR amplification.[3] Direct sequence analysis of PCR products for the caveolin-3 gene was performed using an ABI 377 Sequencer (PE Applied Biosystems, Foster City, CA). The 80 G→A mutation identified in this way was confirmed by analysis of genomic DNA by restriction enzyme digestion with *Bsa*I as described.[4]

Results. By immunohistochemical examinations, dystrophin, α-sarcoglycan, β-dystroglycan, and merosin were normally expressed on muscle fibers. However, the immunoreaction of caveolin-3 and dysferlin was markedly reduced compared with the control (figure 2). Results of Western blot analysis of dysferlin were normal both in size and amount, whereas caveolin-3 was almost absent (data not shown). Sequence analysis of the caveolin-3 gene revealed a G→A substitution on one allele at position 80 causing an amino acid change of an arginine for a glutamine at position 27 (figure 3). We confirmed the mutation with enzyme digestion of PCR products. We did not detect this mutation in 50 normal Japanese control subjects.

Discussion. Mutations in the caveolin-3 gene were first reported in autosomal-dominant limb girdle muscular dystrophy in which the major clinical features were calf hypertrophy and mild to moderate proximal weakness.[3] Two other mutations were reportedly associated with sporadic cases of elevated serum creatine kinase in infants. One of them had a 136 G→A substitution that also caused myalgia and cramps in the lower limbs, without muscle weakness.[5] The other had an 80 G→A substitution that caused asymptomatic elevated serum creatine kinase.[4] The mutation of the caveolin-3 gene in the current case was also an 80 G→A substitution, but the clinical features were different from any cases previously reported.

The term "distal myopathy" is commonly used when distal parts of the limbs are predominantly affected from the early stage of the disease in myopathies. Usually, forearm and leg muscles are affected in addition to hand and foot muscles. For example, in Welander's type distal myopathy, wrist extensor muscles are commonly involved.[7] The tibialis anterior muscles are involved in distal myopathy with rimmed vacuoles, and the gastrocnemius muscles are invariably involved in Miyoshi myopathy.[8,9] In contrast, in the current case, beside slight neck weakness, the muscle atrophy was restricted to the small muscles of the hands and feet. This finding may suggest neurogenic atrophy, but we could not find evidence of neurogenic atrophy using electrophysiologic examinations and biopsy. Because needle electromyography in the hand muscles showed myopathic

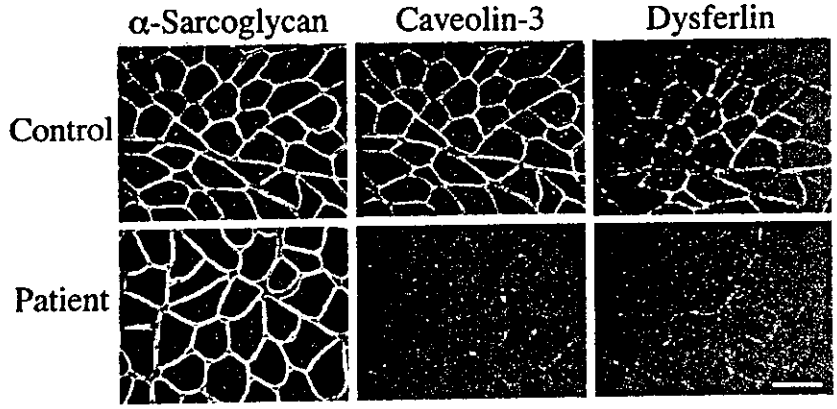

Figure 2. Immunofluorescent staining of skeletal muscles. Normal expression of α-sarcoglycan but reduced expressions of caveolin-3 and dysferlin at the sarcolemma are observed in the patient compared with control. Bar = 100 μm.

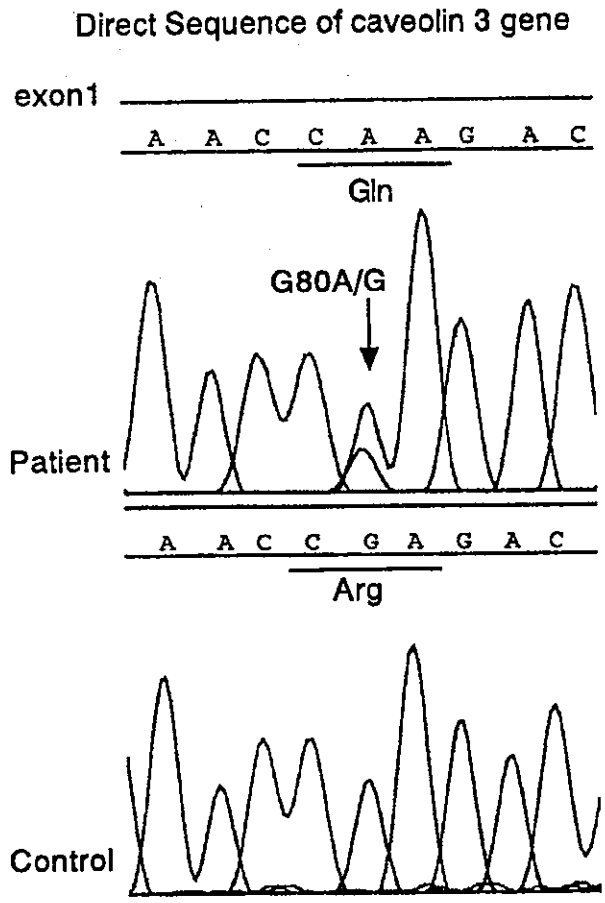

Figure 3. Direct sequence analysis of the caveolin-3 gene. The heterozygous G→A mutation at nucleotide 80 is observed with an amino acid change of the arginine 27 for glutamine (upper panel, arrow). This change is absent in normal controls (lower panel).

motor unit potentials until 12 years of age, we concluded that her muscle atrophy in the small muscles of the hands and feet was caused by myogenic atrophy from the beginning. We think that our patient has unique clinical features distinct from the known types of distal myopathies.

By immunohistochemistry, not only the sarcolemmal expression of caveolin-3 but also that of dysferlin was reduced in the patient. Because results of Western blot analysis of dysferlin were normal, dysferlin expression at the sarcolemma might be secondarily decreased, as reported in sarcoglycanopathies and dystrophinopathies.[10] Our results indicate that caveolin-3 deficiency should also be considered in patients with reduced sarcolemmal expression of dysferlin.

The current case strongly suggests that mutation of the caveolin-3 gene may cause not only myopathies with proximal weakness but also myopathies with distal weakness. This is analogous to cases with mutations in the dysferlin gene that can cause both proximal (limb girdle muscular dystrophy type 2B) and distal muscular dystrophy (Miyoshi myopathy).[9] The distinctions among these clinical phenotypes require the identification of additional factors, such as modifier genes that might reveal the mechanism for muscle involvement.[9] A detailed understanding of the pathogenesis by this mutation in the caveolin-3 gene should highlight the factors that lead to the selective pattern of muscle involvement in muscular dystrophy.

Acknowledgment

The authors thank Mr. Brent Bell for reading this manuscript.

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A Case of Acute Disseminated Encephalomyelitis Presenting Hypersomnia With Decreased Hypocretin Level in Cerebrospinal Fluid

ABSTRACT

A 12-year-old girl was diagnosed as having acute disseminated encephalomyelitis and manifested hypersomnia as the main clinical feature. Magnetic resonance imaging (MRI) revealed lesions in the bilateral hypothalamus in addition to other multifocal brain lesions involving the cerebral white matter, brain stem, and basal ganglia. The level of hypocretin in cerebrospinal fluid was decreased in this patient. Corticosteroid treatment resulted in improvement of the hypersomnia and resolution of MRI lesions in the hypothalamus and other regions. This case suggests that the arousal state control mechanism related to the hypocretin peptide/receptor system may be impaired in some patients with acute disseminated encephalomyelitis. (*J Child Neurol* 2002;17:537–539).

Acute disseminated encephalomyelitis is an acute inflammatory demyelinating disease of the central nervous system, typically characterized by onset of neurologic deficits days to weeks after an episode of viral illness or vaccination.[1] Although the lesions are predominantly located in the periventricular, deep, and subcortical white matter, other whole-brain lesions involving the cortical gray matter, brain stem, basal ganglia, and thalami are frequently observed.[2,3]

Hypocretin (also known as orexin) has recently been recognized as a neuropeptide, and hypocretin deficiency is responsible for idiopathic human narcolepsy,[4] a condition characterized by excessive daytime sleepiness. Narcolepsy or hypersomnia has been reported in demyelinating diseases such as multiple sclerosis[5] and acute disseminated encephalomyelitis,[6] although the precise mechanism remains unknown. We report a case of acute disseminated encephalomyelitis manifesting hypersomnia, hyperintense lesions in the hypothalamus on magnetic resonance imaging (MRI), and decreased hypocretin level in cerebrospinal fluid.

Case Report

A 12-year-old previously healthy girl started to complain of drowsiness several days after an episode of rhinorrhea and low-grade fever. Within a few days, she fell asleep easily even during the daytime, although she was capable of taking a meal by herself and communicating properly with her family. A consulting doctor diagnosed her as having acute disseminated encephalomyelitis from neurologic and brain MRI findings. A T_2-weighted MRI showed multiple foci of high-intensity signal in the midbrain, caudate, putamen, periventricular white matter, and subcortical white matter, and the hypothalamus was also involved (Figures 1 to 3).

Her family history was unremarkable, and she had no recent vaccination. On admission, she could sit in the chair, talk with the examiner, and obey some verbal commands, but she frequently closed her eyes and was nodding off during physical examination. She had no cataplexy and no change of appetite. Her body temperature was 36.6°C, and heart rate and respiratory state were normal. Physical examination revealed no abnor-

Figure 1. Magnetic resonance T_2-weighted parasagittal image shows a high-intensity signal in the posterior hypothalamus (*arrowhead*) in addition to lesions in the anterior thalamus.

Figure 2. Axial T_2-weighted image shows high signal intensity in the right midbrain.

Figure 3. Axial T_2-weighted image shows high signal intensity in the white matter (*large arrowhead*), the bilateral basal ganglia (*arrow*), and the hypothalamus (*small arrowhead*). The high signal intensities in the frontal lobe cortexes are artifacts.

malities. Neurologic evaluation showed hyperactive deep tendon reflexes bilaterally in lower extremities and a positive left extensor response but no abnormalities in cranial nerves and other motor and sensory systems and no symptoms of ataxia and vesicorectal disturbance.

Blood examination showed a white blood cell count of 12 × 10^9/L, C-reactive protein of 0.5 mg/dL, and erythrocyte sedimentation rate of 4 mm/hr. Cerebrospinal fluid analysis revealed a white blood cell count of 33 × 10^6/L (100% lymphocytes), protein and glucose concentrations of 28 mg/dL and 60 mg/dL, respectively, a myelin basic protein level of 57.2 pg/mL (normal < 102 pg/mL), an IgG index of 0.73, and no oligoclonal IgG band. Bacterial and viral cultures of cerebrospinal fluid were negative. Other blood tests were unremarkable, including complete blood cell count, biochemistry, electrolytes, coagulation system, complements, lactic acid, amino acids, blood gas analysis, and antinuclear and anti-DNA antibodies. Serum antiviral antibodies to varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 and antibacterial antibody to *Mycoplasma pneumoniae* indicated no recent infection by these organisms. Human leukocyte antigen typing of this patient was negative for DQB1*0602.

An electroencephalogram (EEG) showed normal basic activity with no slow wave in the waking recordings. She was therefore judged to have no consciousness disturbance. Throughout EEG examination, she could not keep awake without being stimulated verbally. Multiple sleep latency tests revealed a mean sleep latency of 4.5 minutes with no sleep-onset rapid eye movement (REM) periods.

The hypocretin-1 level in cerebrospinal fluid was measured with a ^{125}I hypocretin-1 radioimmunoassay kit (Phoenix Pharmaceuticals, Mountain View, CA). The hypocretin level was decreased (102 pg/mL) compared with the values of age-matched control subjects (238–376 pg/mL).

From the second hospital day, high-dose intravenous methylprednisolone (30 mg/kg) was given for 3 consecutive days followed by oral prednisolone therapy. Her drowsiness gradually decreased from around the initiation of oral prednisolone, and she began to read books or draw her favorite pictures. She no longer noticed drowsiness when she was discharged on the twelfth hospital day. An MRI examination repeated 3 weeks after discharge showed complete resolution of hypothalamic and other lesions, except faintly increased intensity in the bilateral basal ganglia on T_2-weighted images. She remained symptom free during the follow-up period of 1 year. A cerebrospinal fluid examination was not repeated because of complete symptomatic recovery.

The cerebrospinal fluid hypocretin-1 levels were measured in four other patients with acute disseminated encephalomyelitis but no hypothalamic lesions and were found to be within normal limits (data not shown). Of these four patients, two showed consciousness disturbance with abnormal EEGs but did not show hypersomnia, as in the present case.

Discussion

Acute disseminated encephalomyelitis is a monophasic inflammatory demyelinating disease of the central nervous system presenting multifocal neurologic disturbances and an altered consciousness state. Variable degrees of consciousness disturbance were observed in about 70% of patients in large series of acute disseminated encephalomyelitis[2,3]; however, there was no description of hypersomnia in these series. Although the frequency of hypothalamic lesions detected by MRI has not been reported, thalamic involvement was found in up to 40% of patients in previous reports.[2,3] The present case indicates that a patient with acute disseminated encephalomyelitis manifesting hypersomnia might be misdiagnosed as consciousness disturbance owing to cerebral cortex involvement.

Recently, hypocretin cells relating to sleep and arousal regulation have been demonstrated in the posterior thalamus and rostral midbrain, and these regions have been speculated to constitute the "waking center"[7] because many hypersomnolent or narcoleptic patients associated with lesions of the diencephalon have been reported. In the present case, it is reasonable to consider that hypersomnia could have resulted from impaired control of the arousal state, judging from the normal EEG in the waking state and the posterior hypothalamic lesion on MRI. We speculate that the acute disseminated encephalomyelitis lesions can injure the hypocretin cells in the posterior hypothalamus, resulting in dysfunction of the hypocretin system and decreased cerebrospinal fluid hypocretin level. To our knowledge, this is the first report of a decreased hypocretin level in a demyelinating disease manifesting hypersomnia.

Recent studies have demonstrated that genetic alterations in the preprohypocretin or hypocretin receptor 2 gene induce narcolepsy in animals.[8,9] Although the involvement of hypocretin-related genes is rare in human narcolepsy, a series of studies that measured hypocretin contents in cerebrospinal fluid and brain suggest that a deficit in hypocretin neurotransmission is involved in most cases.[4,10] Since a reduction of hypocretin in the cerebrospinal fluid is likely to reflect the major pathophysiology of the disease in humans, measuring cerebrospinal fluid hypocretin levels may thus become a standard diagnostic tool for narcolepsy.[11]

Decreased cerebrospinal fluid hypocretin levels have also been recognized in symptomatic narcolepsy after a diencephalic stroke[12] and hypersomnolence after removal of a hypothalamic tumor.[13] However, a decreased hypocretin level has not been described in inflammatory demyelinating disorders.[14] Further, our four other patients with acute disseminated encephalomyelitis also had normal hypocretin levels. However, the evaluation of the cerebrospinal fluid hypocretin levels in patients with acute disseminated encephalomyelitis has just begun; further investigations will elucidate the significance of hypocretin in the pathophysiology of acute disseminated encephalomyelitis.

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Received Feb 5, 2002. Received revised April 8, 2002. Accepted for publication April 16, 2002.

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Children With Irreversible Brain Damage Associated With Hypothyroidism and Multiple Intracranial Calcifications

ABSTRACT

Children who develop clinical hypothyroidism in early childhood have various degrees of irreversible brain damage, albeit less severe than cases detected by neonatal screening test for hypothyroidism in the first months of the life. We report three patients with hypothyroidism of childhood onset after a normal neonatal thyroid-stimulating hormone screening who showed deceleration in linear growth, spasticity in the lower limbs with deformity, mild intellectual impairment, and multiple calcifications in the basal ganglia and subcortical areas. The neurologic symptoms were not progressive but were irreversible in spite of thyroxine treatment. Motor disturbances commonly observed in postnatal-onset hypothyroidism are similar to those of cerebral palsy. Specific distribution of

intracranial calcifications may result from metabolic derangement as a result of hypothyroidism, although the mechanism of calcification is not fully understood. We emphasize the need to re-evaluate thyroid function in diplegic patients with specific intracranial calcifications but normal neonatal thyroid-stimulating hormone screening. (*J Child Neurol* 2002;17:309–313).

Most cases of infantile hypothyroidism caused by thyroid dysgenesis can be detected by thyroid-stimulating hormone screening of the newborn and are successfully treated with immediate hormone replacement. However, a small number of children with subclinical hypothyroidism, pituitary-origin hypothyroidism, a late increase in thyroid-stimulating hormone,[1,2] or acquired autoimmune hypothyroidism[3] are normal in neonatal screening, and onset of overt hypothyroidism is rarely detected before the age of 3 years. Thyroid hormones have been recognized to play an important role in the growth, development, and maturation of the nervous system.[4] Failure in early diagnosis and treatment of congenital hypothyroidism may cause permanent motor, mental, and neuropsychologic dysfunction of the central nervous system.[5] In this report, we describe three cases of hypothyroidism with childhood onset after a normal neonatal thyroid-stimulating hormone screening who manifested progressive spasticity in the lower limbs and intracranial calcifications since infancy. We emphasize the importance of thyroid function re-evaluation in diplegic patients with a diagnosis of cerebral palsy.

Case Report

Patient 1

Patient 1 was a 5-year-old girl who was clinically evaluated because of retarded psychomotor development, deceleration in linear growth after the age of 9 months, and progressive spasticity in the lower limbs. The girl was born at term after an uncomplicated pregnancy, 2600 g in weight and 49.5 cm in length. Her mother showed neither symptoms suggesting gestational hypothyroidism nor a history of taking iodine-containing medicines. The fontanelles were normally patent at birth. The result of neonatal screening for hypothyroidism was normal. Developmental milestones were delayed: head control was reached at 6 months and sitting at 12 months. She was able to stand with support at 3 years of age but became unable to stand a year later because of severe joint deformities in the lower limbs, including the talipes equinovarus. Physical examination at 5 years of age revealed abnormal growth at 10 kg in weight (–3 SD) and 85 cm in height (–5.6 SD), coarse facial features, hoarseness, and congenital right ptosis. Spastic diplegia and rigidity with exaggerated deep tendon reflexes and delayed relaxation phase of ankle jerk were found. Bilateral joint contractures of the ankle, knee (Figure 1A) and hip, together with dorsiflexed plantar response, were noted. Tremor and dystonia were not seen. Fine motor coordination of hands was poor. Truncal hypotonia was present without muscle wasting. Sensation, cranial nerves, coordination, hearing, and vision were intact. The thyroid gland was not palpable. The IQ on the Wechsler Intelligence Scale for Children-Revised (WISC-R) was 46. Serum concentration of free triiodothyronine was 0.6 pg/mL (normal = 2.47–4.34 pg/mL), and free thyroxine was less than 0.2 ng/dL (normal = 0.97–1.79 ng/dL). Thyroid-stimulating hormone was 165 μU/mL (normal = 0.34–3.5 μU/mL). Serum creatine kinase level and total cholesterol were elevated at 924 IU/L and 296 mg/dL, respectively. The thyroid was mildly small by volume by ultrasonographic scan, and a technetium thyroid scan showed normal location. Thyroid radioiodine uptake was markedly decreased to 2% at 24 hours (normal = 12–30%). Maternal antibodies were not examined, but there was no family history of autoimmune thyroid disease. Serum microsome test, thyroid test, antinuclear antibody, anti-DNA antibody, and thyrotropine-receptor antibody were positive and remarkably high. Her bone age was 2½ years. Nerve conduction velocities in the extremities and protein level in the cerebrospinal fluid were normal. Brain computed tomography (CT) showed multiple calcifications in the bilateral basal ganglia and subcortical areas in the occipital lobes. Magnetic resonance images (MRIs) showed delayed myelination without abnormal intensity. Intravenous pyelography showed dilation of bilateral ureters. Renal echogenicity was abnormal. Treatment with thyroxine improved growth and normalized serum creatine kinase level, total cholesterol, and thyroid hormone levels, but clinical findings such as spasticity and deformation in the lower limbs, abnormal mental development, and intracranial calcifications remain unchanged.

Patient 2

Patient 2 was a 5-year-old boy who had goiter and delayed bone age (1½ years). He was born at term with mild asphyxia, 3250 g in weight and 49.5 cm in length. The result of neonatal screening for hypothyroidism was normal. His developmental milestones were delayed, and he only started to stand with support at 18 months of age. Spastic cerebral palsy was diagnosed. Brain CT scan revealed calcifications of the bilateral basal ganglia and subcortical area in the occipital lobes. At the age of 5 years, repeated evaluation of thyroid function tests consistently showed normal triiodothyronine, thyroxine levels and a slightly elevated thyroid-stimulating hormone level, 10.1 μU/mL. A thyrotropin-releasing hormone test showed an abnormal hyper-response of thyroid-stimulating hormone, 67.9 μU/mL at 30 minutes and 58.4 μU/mL at 60 minutes. Serum creatine kinase level was 28 IU/L, and total cholesterol was 144 mg/dL. Subclinical hypothyroidism was suspected. He had spastic diplegia and rigidity with flexor contractures of the knees and talipes equinovarus of the ankles (Figure 1B). At age 8 years, he had anemia, thrombocytopenia, and nephrotic syndrome associated with positive Coombs's test and elevated antiplatelet and antinuclear antibodies. At age 15 years, he was re-evaluated for thyroid function because of goiter, deceleration in linear growth after the age of 18 months, and slowly progressive joint contractures in the lower limbs, including the talipes equinovarus. Physical examination showed coarse facial features and hoarseness. Exaggerated tendon reflexes with positive plantar responses and contractures of the ankle and knee were noted. Sensation, cranial nerves, coordination, hearing, and vision were intact. Tremor and dystonia were not seen. His IQ was 58. Serum triiodothyronine, thyroxine, and thyroid-stimulating hormone levels were abnormal at 45 ng/dL (normal = 70–180 ng/dL), 2.7 μg/dL (normal = 5.2–12.4 μg/dL), and 37.8 μU/mL, respectively. Ultrasonographic thyroid scan was normal by volume and location. Magnetic resonance images were normal. Maternal antibodies were not examined. There was no family history of autoimmune thyroid disease. Serum microsome test (1:400) and thyroid test (1:100) were positive. Treatment with thyroxine was initiated. There was no improvement of motor and mental dysfunction.

Patient 3

Patient 3 was a 3-year-old girl who exhibited mildly abnormal thyroid function. Subclinical hypothyroidism was suspected at the age of 2 years based on serum levels of free thyroxine at 1.0 pg/mL and thyroid-stimulating hormone at 6.3 μU/mL, and she was treated with thyroxine. She was born at term after an uncomplicated pregnancy, 2926 g in weight and 46 cm in length. The results of neonatal screening for hypothyroidism were normal. Physical examination revealed shortness of stature, small hands and feet with short fifth digits, coarse facial features, and hypertrichosis. She was unable to walk unaided owing to truncal hypotonia and symmetric spasticity in the lower limbs with exaggerated deep tendon reflexes. Bilateral plantar responses were positive. Knock-knees with wide base and everted feet were noted while walking with support. No extrapyramidal and cerebellar signs were observed. Fine motor development of the hands, hearing, and vision were intact. Ultrasonographic thyroid scan was normal by volume and location. Brain CT showed calcifications on the bilateral basal ganglia and subcortical area in the occipital lobes (Figure 2), but MRIs were nor-

Figure 1. Spasticity in lower limbs with severe contractures of the knees and ankles in patient 1 (*A*) and patient 2 (*B*).

mal. Serum creatine kinase level and total cholesterol were within normal ranges. Maternal antibodies were not examined. Autoimmune antibodies were negative except for a mild elevation of thyroid stimulation blocking antibody (18.1%). Her IQ was 65. There was no family history of autoimmune thyroid disease. After 1 year of hormonal replacement, she remained unable to walk, but there was no progression of leg deformity and mental retardation.

Discussion

We reported three patients who were normal in neonatal thyroid-stimulating hormone screening but developed various degrees of hypothyroidism in infancy. These patients showed a broad spectrum of severity in neurologic symptoms, but all had the common clinical characteristics of hypothyroidism, deceleration in linear growth, spasticity or rigidity in the lower limbs with deformity, mild intellectual impairment, and multiple calcifications on the basal ganglia and subcortical areas. The evidence of thyroid antibodies in patients 1 and 2 suggests that acquired hypothyroidism may be caused by an autoimmune mechanism. Complications in these two patients, such as renal disease, hemolytic anemia, and idiopathic thrombocytopenia, may result from the underlying autoimmune disease. In patient 3, who had small hands and feet as well as other minor anomalies but no evidence of thyroid antibodies, hypothyroidism may be associated with underlying multiple dysmorphogenesis.

A variety of motor disturbances in human thyroid diseases are shown in Table 1.[6-10] Hypothyroidism with early childhood onset is characterized by spasticity as a dominant clinical feature among neurologic symptoms and poor response to hormonal replacement therapy. The spectrum of neurologic disturbances owing to

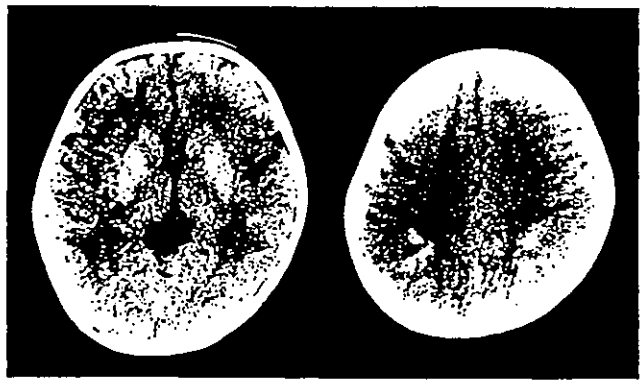

Figure 2. Brain computed tomogram of patient 3 showing multiple calcifications in the bilateral basal ganglia (*left*) and subcortical white matter in the occipital lobes (*right*).

Table 1. Summary of Neurologic and Radiologic Findings and Response to Treatment in Hypothyroidism

	Spasticity in the Lower Limbs	*Basal Ganglia Calcification*	*Neurologic Symptoms and Signs*	*Response to the Treatment*	*Reference No.*
Endemic cretinism	89%	30%	Mental retardation, pyramidal tract signs in the lower limbs, extrapyramidal tract signs	Poor, not improve neurologic status	6, 7, 9, 10
Congenital hypothyroidism	30%	Rare	Truncal hypotonia, peripheral neuropathy, incoordination, cerebellar ataxia, mental deterioration	Possible, depending on the severity and duration of the hypothyroxemia	6, 9, 10
Myxedema	Rare	Possible	Muscle weakness, cerebellar ataxia, sensory neuropathy, somnolence, psychosis	Fair	6, 8
Patients in this study	3/3	3/3	Pyramidal tract signs in the lower limbs, joint contractures, mental retardation, hypotonia	Not improve neurologic status	

thyroid hormone deficiency in the immature brain depends on the sequence and timing of normal neuroanatomic development of the motor system.[9] Eighty-nine percent of patients with endemic cretinism were reported to exhibit spasticity through damage to specific cortical areas and the corticospinal tract.[7,9] Thirty percent of patients with sporadic congenital hypothyroidism, untreated or treated over a few months after birth, were reported to have motor dysfunctions including fine motor clumsiness, spasticity, pyramidal tract signs, and poor coordination,[6,10,11] resulting from lesions in the primary motor cortex.[9] Furthermore, both maternal hypothyroidism and hyperthyroidism during pregnancy may be associated with a 20-fold increase in risk for the development of cerebral palsy in the progeny through transient fetal hypothyroxinemia.[12,13] Neuropathologic findings in the brains of patients with endemic cretinism, congenital hypothyroidism, and fetal hypothyroidism owing to maternal hypothyroidism have been found to be similar to those observed in cerebral palsy. Findings in congenital hypothyroidism and endemic cretinism include minimal cerebral atrophy, reduced number of pyramidal and Betz neurons in layer V, and abnormal axonal and dendritic development of the pyramidal neurons in the cerebral cortex and brainstem.[4,9,10,14] Therefore, it is possible that motor disturbances commonly observed in hypothyroidism with prenatal, perinatal, or even early postnatal onset are similar to those of cerebral palsy.

Neonatal thyroid-stimulating hormone screening is very useful for early diagnosis of congenital hypothyroidism so that thyroxine treatment can be initiated as early as possible to prevent neurologic sequelae. However, in patients with subclinical hypothyroidism, as in patients 2 and 3, and acquired hypothyroidism owing to autoimmune mechanism, as in patients 1 and 2, the screening test may be invalid because overt hypothyroidism may develop later in infancy or childhood. It has been believed that once the nervous system has reached full maturity, the effect of thyroid hormones on the brain is minimal.[3] However, even early diagnosis and treatment of hypothyroidism cannot prevent abnormal neurologic and neuropsychologic development in some children for unknown reasons.[9] Postnatal brain development can be adversely affected by inadequate thyroxine treatment, poor drug compliance, or the presence of irreversible fetal and postnatal neuropathologic changes.[9] Pediatricians and neurologists should be aware that untreated mild hypothyroidism and postnatal-onset hypothyroidism can cause motor or mental abnormalities easily misdiagnosed as cerebral palsy.

The main causes of basal ganglia calcifications in infancy and childhood are inflammatory, neoplastic and dysplastic, vascular, hypoxic, endocrine, toxic, metabolic, and degenerative diseases.[5] In the patients of this study, intrauterine infections, drugs, toxins, and metabolic and endocrine disorders, except hypothyroidism, were excluded by laboratory data or medical history. Some causes of intracranial calcifications can be speculated, such as latent hypoxic damage, vasculitis, and direct brain insult owing to energy insufficiency caused by hypothyroidism. In previous studies, the correlation between basal ganglia calcifications and spasticity or other neurologic symptoms in endemic cretinism are controversial,[7,15] although they are found in asymptomatic or nonspecific symptoms such as dementia in adult-onset myxedema.[8] However, as shown in Table 1, the frequency of hypothyroidism-associated intracranial calcifications is 30% in endemic cretinism,[7] and four of six adult patients with unexplained intracerebellar calcifications showed hypothyroidism.[5] Therefore, the intracranial calcifications may result from metabolic derangement as a result of hypothyroidism. Although the mechanism of calcifications is not fully understood, microangiopathy has been suggested as a pathologic background. Magnetic resonance images have demonstrated hyperintensity on T_1-weighted and hypointensity on T_2-weighted in the basal ganglia in endemic cretinism,[16] and a neuropathologic study of congenital hypothyroidism has demonstrated that cerebral blood vessels are thickened with calcium and iron deposits.[17]

Finally, even with normal neonatal thyroid-stimulating hormone screening findings, we emphasize the need to reconsider the diagnosis of hypothyroidism in children exhibiting spasticity in the lower limbs and deceleration in linear growth, or multiple calcifications in bilateral basal ganglia and subcortical areas on brain CT. There is no convincing evidence for neurologic prognosis, although the neurologic manifestations of the patients in this study were neither progressive nor reversible after thyroxine treatment. The pathophysiology and plasticity of the brain in hypothyroidism

remain unknown, and further investigations are needed to elucidate the critical period of irreversible brain damage.

Acknowledgment

We thank Dr. M. Minagawa of the Graduate School of Medicine, Chiba University, for providing helpful comments.

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Received Nov 29, 2001. Received revised Jan 30, 2002. Accepted for publication Feb 11, 2002.

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CME

Clinical and pathologic characteristics of nontyphoidal salmonella encephalopathy

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Abstract—*Objective:* To investigate the clinical and pathologic characteristics of primary encephalopathy caused by nontyphoidal salmonellosis (NTS). *Methods:* Case records of six Japanese hospitals from 1994 to 1999 were reviewed. Eight cases of primary NTS encephalopathy were identified based on strictly defined criteria: 1) encephalopathic feature defined as altered state of consciousness, altered cognition or personality, or seizures; 2) detection of nontyphoidal *Salmonella* species in stool; 3) absence of other viral or bacterial infection associated with CNS abnormalities; and 4) absence of alternative explanation by underlying neurologic or systemic disease. Three patients died, three had severe sequelae, and two recovered completely. The authors analyzed their clinical course, neurologic symptoms, and histopathologic findings. *Results:* NTS encephalopathy was clinically characterized by diffuse and rapidly progressive brain dysfunction and circulatory failure that developed following enteritis. There was no evidence of severe dehydration or sepsis, and encephalopathy was rarely accompanied by abnormal laboratory data, except elevated CSF opening pressure, brain edema on CT, and slow waves on EEG. Pathologic findings included minimal ischemic damage and mild edema in the brain, microvesicular fatty change of the liver, severe enterocolitis but no evidence of dehydration, and no fatal organ damage including microvasculature and endothelial cells. *Conclusion:* Noninfectious encephalopathy associated with nontyphoidal salmonella infection is a distinctive clinical entity that can be differentiated from Reye's syndrome and Ekiri.

NEUROLOGY 2002;58:1641–1645

Nontyphoidal salmonellosis (NTS) is a common form of food poisoning caused mainly by *Salmonella enteritidis*. The incidence is increasing worldwide due to contaminated eggs. Extraintestinal manifestations of gastrointestinal infections are important clinically. Whereas some of these infections manifest via systemic dissemination and direct colonization of the CNS,[1,2] we previously reported the possibility of primary encephalopathy associated with NTS (NTS encephalopathy)[3] and suggested that the organisms might affect brain function via remote and undetermined mechanisms. Recently, *S. enteritidis* infection has become a public health problem in the United States, with 380 outbreaks reported from 1985 to 1991, involving 13,056 patients and 50 deaths.[4] Epidemiologic data of serious neurologic conditions associated with NTS are poorly documented, because this complication has received little attention.

Methods. Case records of six Japanese hospitals from 1994 to 1999 were reviewed. Eight cases of NTS encephalopathy were identified, which met the following criteria: 1) encephalopathic feature, defined as one of the following altered state of consciousness, altered cognition or personality, or seizures[5]; 2) detection of nontyphoidal *Salmonella* species in stool; 3) absence of other viral or bacterial infection associated with CNS abnormalities; and 4) absence of an alternative explanation by underlying neurologic or systemic disease. Patients were excluded if they had factors that could secondarily induce encephalopathy, such as se-

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Received September 10, 2001. Accepted in final form February 22, 2002.

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Table Summary of clinical findings in nontyphoidal salmonella encephalopathy

Characteristics	Patient no. 1	2	3	4
Age, y/sex	3/F	6/M	7/F	6/M
Bacteriology	*S. enteritidis*	*S. enteritidis*	*S. enteritidis*	*S. enteritidis*
Phage type	O9	O9	NA	O9
Prodromal symptoms	F, V, D	F, V, D	F, V, D	F, V, D
Latent period	12 h	17 h	18 h	16 h
Degree of dehydration, %	3	5	NA	8
Initial neurologic symptom	Seizure	LOC	LOC	LOC
Neurologic symptoms and signs (at the advanced stage)	Coma	Coma	Coma	Coma, decerebrate posture, hyperventilation
CSF opening pressure, mmH_2O	160	100	200	220
Circulatory failure?	No	Mild	Moderate	Moderate
Required mechanical ventilation?	No	No	No	No
Other complications†	No	ARF	Hypotension, ARF, decreased PLT, rhabdomyolysis, liver dysfunction	Hypotension, ARF, decreased PLT, rhabdomyolysis, liver dysfunction
Duration of encephalopathic features	4 d	5 d	13 d	20 d
Outcome	Full recovery	Full recovery	Spastic quadriplegia	Spastic quadriplegia

* Serogroup was C.
† After the onset of neurologic symptoms.
‡ Brain death on the fifth hospital day.

F = fever; D = diarrhea; V = vomiting; LOC = loss of consciousness; NA = not available; ARF = acute renal failure; PLT = platelet.

vere dehydration, sepsis, meningitis, localized suppurative infections or viral encephalitis, hyponatremia and other electrolyte and metabolic disturbances, hypocalcemia, hyperammonemia, hypoglycemia, and lactic acidemia. "Severe dehydration" was defined as body fluid deficit of 10% or more, and was clinically estimated based on the following general conditions: body weight loss >10%, decreased skin elasticity indicated by slow pinch retraction, grossly sunken eyes, absence of tears, very dry mucous membranes, and very little urine flow.[6]

Blood culture was performed on all patients, including postmortem samples. Serum endotoxin was measured in four patients using Endotoxin Single Test (Wako Pure Chemicals Ind., Osaka, Japan). Verotoxin-1 and verotoxin-2 were examined immunologically with agglutination method (Denka Seiken, Tokyo, Japan) in the isolated *S. enteritidis* from Patient 4. Hematologic and biochemical tests were conducted in six patients (except Patients 5 and 6, who died unexpectedly) at the onset of neurologic symptoms. Three of the eight patients died. Autopsies were performed on two patients who died within several hours of disease onset.

Results. The table summarizes the clinical data of patients with NTS encephalopathy. Patients 1 and 4 have been described previously.[3]

Case presentation. Patient 6. A 14-year-old boy presented with frequent diarrhea, abdominal pain, and fever that had lasted 28 hours. Four members of his family had enteritis. He had rested in bed without receiving any medical treatment, and could drink water by himself. He had no headache or vomiting, and responded to verbal stimulation. His level of consciousness seemed to decrease gradually in the subsequent several hours. He died unexpectedly 8 hours later. Dehydration was mild, judging from 5% weight loss, skin elasticity, and mucous dryness. Bacteremia was not found. Endotoxin was not examined. *S. enteritidis* phage type 1 was isolated from his stool. He was autopsied and investigated pathologically.

Patient 7. A 3-year-old boy presented with generalized seizure and lethargy after remission from an 11-day history of diarrhea. He showed no signs of circulatory failure. Laboratory examinations of blood and CSF showed no abnormalities. After admission, he developed stupor, followed by increased bilateral deep tendon reflexes with ankle clonus, conjugate deviation of the eyes to the left, acute renal failure, and thrombocytopenia. Several months later, he showed moderate mental retardation. *S. enteritidis* phage type 9 was isolated from his stool on the first and 13th hospital day, but not from the CSF or blood. EEG exhibited 5 to 8 Hz slow waves dominantly in the right occipital area on the 16th hospital day. Cranial MRI showed diffuse edema without focal lesions.

Clinical findings. All eight cases were previously healthy Japanese children. The causative organism was *S. enteritidis* except in one case. *S. enteritidis* phage type 9 was found in four patients, type 1 in one, and was unidentified in two. Diarrhea, fever, and vomiting were common prodromal symptoms. Six patients presented encephalopathic features within an average of 20 hours of onset of an enteric episode associated with NTS. Two patients exhibited neurologic symptoms from the 10th to 13th day of the illness. Initial neurologic symptoms included altered