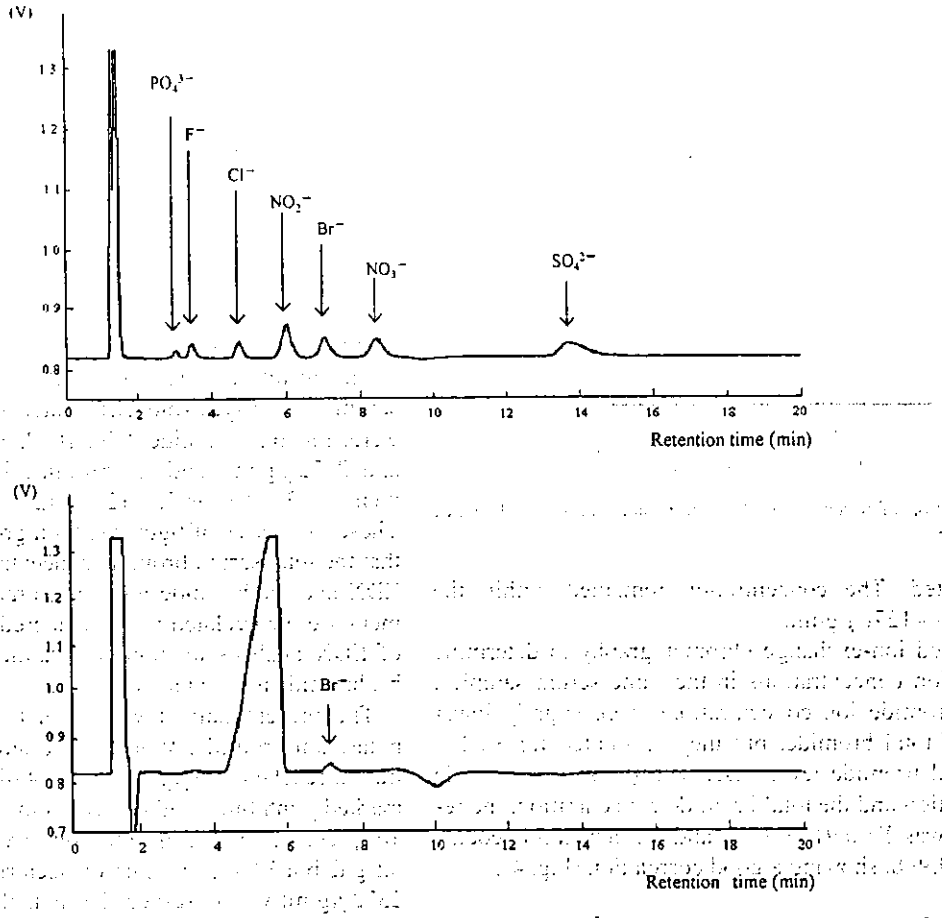

Fig. 2. Upper Panel: Chromatogram of Anion Standard Solution Containing 0.04 μg/ml of PO_4^{3-}, 0.02 μg/ml each of NO_2^-, Br^-, NO_3^-, and SO_4^{2-}, and 0.004 μg/ml each of F^- and Cl^-
Lower Panel: Chromatogram of Standard Serum with Bromide Added to Yield a 10 μg/ml Bromide Ion Solution

complete one analysis, including the time taken to separate the serum from the sample, was 20 min.

Bromide Ion Determination by HPLC The standard bromide ion curve obtained through ion-exchange chromatography, within the range 0.05—200 μg/ml, yielded a regression line between area and concentration of $Y=27369X-3027$, with a correlation coefficient of $r=0.999$. Samples with concentrations higher than the range of the standard curve were diluted with distilled water before being analyzed. The lower limit of determination for bromide ion solutions was 0.05 μg/ml, and when the signal-to-noise ratio was taken as 5, the detection limit was 0.01 μg/ml.

A chromatogram of the standard negative ion solution and a chromatogram using a sample that was added to obtain a standard serum with a final bromide concentration of 10 μg/ml bromide ion is shown in Fig. 2. No interference peaks can be seen, and good separation was obtained for bromide ion. The mean recovery rate was 99.6±1.3% ($n=5$), and one analysis, including pretreatment, took 40 min.

Bromide Analysis in Patient Serum and Relationship between Serum Total Bromide Concentration and Bromide Ion Concentration A graph showing the relationship between the potassium bromide dose and the serum total bromide in the 10-year-old patient is shown in Fig. 3. Administration started at a dose of 1.0 g/d, and the serum total bromide concentration on the 44th day before the morning dosing was 899 μg/ml. During this period, the patient's epileptic

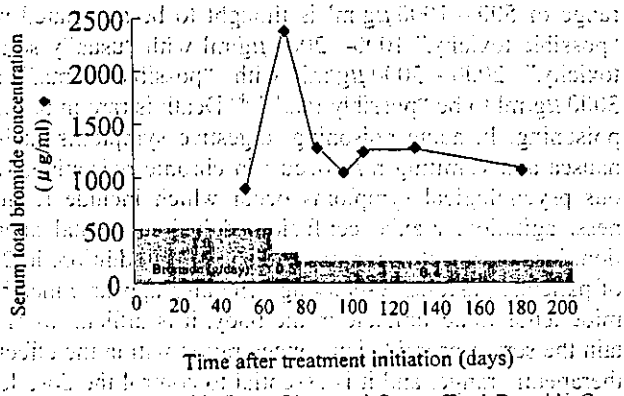

Fig. 3. Potassium Bromide Dose Given and Serum Total Bromide Concentration in a 10-Year-Old Patient

seizures were well controlled, and no effect was seen on her daily activities. To maintain control at about this concentration, the dose was decreased to 0.5 g/d from day 63. However, before the morning administration on day 77, the serum total bromide was found to be 2372 μg/ml, an unexpectedly high level. Fortunately, during that time, no neurological or psychological symptoms that could be considered due to chronic poisoning were observed. From the 77th day the dose was reduced to 0.4 g/d, and on day 89 the serum total bromide concentration was 1276 μg/ml. The dosage was not changed again, and periodic analysis of the total bromide

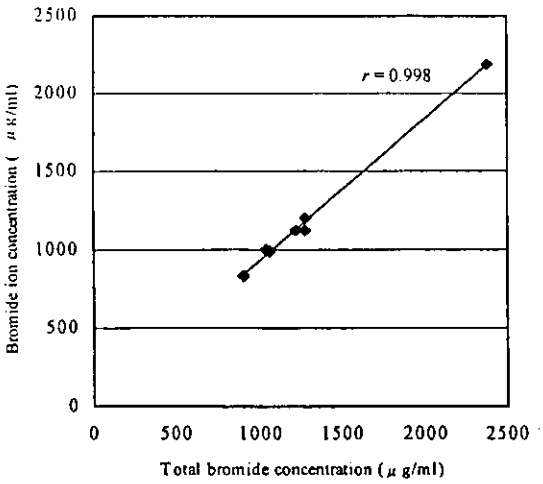

Fig. 4. Correlation of Serum Total Bromide Concentration and Bromide Ion Concentration

were conducted. The concentration remained within the range of 1032—1276 μg/ml.

We also used ion-exchange chromatography to determine the bromide ion concentrations in the same serum samples. The serum bromide ion concentrations were slightly lower than those of total bromide, but they accounted for 88.2—96.7% of total bromide levels. Between the serum bromide ion concentration and the total bromide concentration, the regression line was $Y=0.91X+17.3$, and the correlation coefficient was $r=0.998$, showing a good correlation (Fig. 4).

DISCUSSION

A serum bromide ion concentration of up to 500 μg/ml is considered to be the therapeutic dose range, but the dose range of 500—1000 μg/ml is thought to be associated with "possible toxicity," 1000—2000 μg/ml with "usually serious toxicity," 2000—3000 μg/ml with "possible coma," and 3000 μg/ml to be "possibly fatal."[7,8] Death is rare in bromide poisoning. In acute poisoning, digestive symptoms such as nausea and vomiting may occur; in chronic poisoning, various psychological symptoms occur which include restlessness, agitation, ataxia, confusion, delusion, mental aberration, loss of muscle strength, and stupor. In addition, in 25% of patients, pustules resembling acne also appear. Since bromide tends to accumulate in the body, it is difficult to maintain the serum bromide ion concentration within the effective therapeutic range, and it is essential to control the dose level by monitoring the serum level.[4]

In the present study, we performed analysis of the serum total bromide concentration using EDX. The standard curve using the bromide $K\alpha$ line exhibited good linearity for serum total bromide concentrations from 10 to 2000 μg/ml, and within this range of concentrations qualitative analysis was performed with ease using the EDX spectrum. The pretreatment procedures were simple and satisfactory: after the serum was centrifuged, it was dripped onto filter paper, and then the paper was dried. The mean recovery rate of bromide added to the serum in amounts in the range of 50—2000 μg/ml was 93.5% or more. The method was fast, and the time required for one analysis, including the separation of the serum from the whole blood, was no more than 20 min.

The pharmacological actions of bromide are correlated with the concentration of bromide ions in the blood.[7,8] We therefore performed an analysis of bromide ions by anion ion-exchange chromatography and investigated whether the results of total bromide analysis by EDX were correlated with those of bromide ion analysis. A good linear standard curve was obtained using HPLC for bromide ion concentrations between 0.05 and 200 μg/ml, and a satisfactory value of 99.6% was achieved for the mean recovery rate of 10 μg/ml of bromide ion added to the serum. However, the time taken for one analysis, including that for pretreatment, was over 40 min, which was twice that needed for EDX.

The results of analysis using these two methods for the serum of a 10-year-old girl treated with potassium bromide were: for total bromide, 899, 1032, 1061, 1219, 1271, 1276, and 2372 μg/ml; and for bromide ions in the same specimens, 833, 981, 997, 1126, 1126, 1197, and 2187 μg/ml. These two series of figures exhibit good correlation. The fact that the total serum bromide concentrations determined using EDX and the bromide ion concentrations in the same specimens were correlated was considered to indicate that the use of EDX analysis to monitor treatment with, and poisoning by, bromide is a viable possibility.

The present patient was at first administered 1.0 g/d of potassium bromide. When the serum total bromide concentration reached 899 μg/ml on the 44th day, the seizures were markedly inhibited and no symptoms of poisoning were seen. To preserve this concentration, we reduced the dose to 0.5 g/d, but 33 d later an unforeseen rise to a concentration of 2372 μg/ml was observed. No notable symptoms of toxicity were seen, but determination of the serum content permitted a judgment on dose reduction. After the dose was decreased to 0.4 g/d, the concentration reached and maintained a favorable serum level of total bromide. In this patient, there was some difficulty in controlling the pharmacological effect from the dose level of bromide, and thus a rapid technique for determining the serum level of bromide is a useful tool.

It has now become possible to monitor treatment with bromide simply and quickly and to verify the appropriateness of treatment by analyzing the total bromide concentration using EDX. Our intention is now to work on drug treatment design by calculating the pharmacokinetic variables of bromide to prevent cases of poisoning.

REFERENCES

1) Locock C., *Lancet*, **1**, 527—528 (1857).
2) Livingston S., Pearson P. H., *Am. J. Dis. Child.*, **86**, 717—720 (1972).
3) Ernst J. P., Doose H., Baier W. K., *Brain Dev.*, **10**, 385—388 (1988).
4) Olson K. R., "Bromides: Poisoning & Drug Overdose," 3rd ed., Dempsey DA, San Francisco, 1998, pp. 115—117.
5) Woodbury D. M., Kemp J. W., "Psychopathology and Brain Dysfunction," ed. by Shagass C., Gershon S., Friedhoff A. J., Raven Press, New York, 1977, pp. 149—182.
6) Woodbury D. M., Pippenger C. E., "Antiepileptic Drugs," Raven Press, New York, 1982, pp. 791—801.
7) Palatucci D. M., *Neurology*, **28**, 1189—1191 (1978).
8) Elin R. J., Robertson E. A., Johnson E., *Clin. Chem.*, **27**, 778—779 (1981).
9) Soremark R., *Acta Physiol. Scand.*, **50**, 119—123 (1960).
10) Livingston S., "Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence," Charles Thomas, Springfield, 1972, pp. 268—274.
11) Notkin J., *Arch. Neurol. Psychiat.*, **21**, 165—178 (1929).

12) Palmer J. W., Clarke H. T., *J. Biol. Chem.*, **99**, 435—444 (1933).
13) Ulrich A., *Med. J. Rec.*, **126**, 41—42, 88—90, 156—158 (1927).
14) Shimomura S., Kabasawa Y., "Instrumental Analysis." Hirokawa, Tokyo, 1997.
15) Namera A., Namiki K., *Chudoku Kenkyu* (*Jpn. J. Toxicol.*), **13**, 91—97 (2000).
16) Goshi Y., Sato K., "Energy Dispersive X-ray Analysis," Gakkai Shuppan Center, Tokyo, 2001.
17) Ruan S., Gu Z., Yang Y., *Zhonghua Yu Fang Yi Xue Za Zhi*, **33**, 107—109 (1999).
18) Nasstrom K., Odselius R., Petersson A., *Scanning Microsc.*, **10**, 339—347 (1996).
19) Kodaka T., Mori R., Sano T., Debari K., *J. Electron Microsc.*, **44**, 289—294 (1995).

Original Article

Vitamin K Deficiency in Severely Disabled Children

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ABSTRACT

Vitamin K status was examined in 21 severely disabled children in our hospital from September 2001 to August 2002, and 9 children were found to have a vitamin K deficiency. The 21 patients were divided into two groups: group A, 9 patients with vitamin K deficiency, and group B, 12 patients without vitamin K deficiency. The laboratory data and background factors in the two groups were compared statistically. In group A, all patients received enteral nutrition and anticonvulsants. The protein induced by vitamin K absence-II values were elevated in eight patients. Seven exhibited a bleeding tendency. Six developed vitamin K deficiency in association with infection and four were treated with antibiotics. All showed a good response to the administration of vitamin K. The patients in group A had factors such as use of antibiotics, infection, and elemental nutrition at significantly higher rates than those in group B. Data indicating nutrition factors such as body weight, caloric intake, total protein level, and hemoglobin level were not significantly different between the two groups. Severely disabled children suffer from deficiencies of various nutritional elements. However, vitamin K deficiency in severely disabled children has not been fully investigated. Infection, use of antibiotics, and elemental nutrition are risk factors for vitamin K deficiency in severely disabled children. In severely disabled children, there might be marginal vitamin K intake via enteral nutrition, so more vitamin K supplementation is necessary, especially with infection and use of antibiotics. (*J Child Neurol* 2003;18:93–97).

Severely disabled children suffer from various complications.[1] A bleeding tendency is sometimes seen in severely disabled children and is considered to be caused mainly by reflux esophagitis, a gastric and/or duodenal ulcer, or oozing from granulation tissue around the tracheotomy or gastrostomy tube. Mucosal damage is also easily caused by a suction tube or change of the tracheotomy tube. Most cases are diagnosed as having gastrointestinal bleeding owing to gastroesophageal reflux or mucosal damage until the correct diagnosis is made. In particular, when a patient is without antibiotics and diarrhea, vitamin K deficiency is easily misdiagnosed as another gastric complication. Although vitamin K deficiency has not been considered to be a rare complication in severely disabled children, it has not been fully investigated. On the other hand, vitamin K is present at exceptionally low concentration in serum, and its deficiency is difficult to quantify. In vitamin K deficiency, it is detectable as an abnormal form known as protein induced by vitamin K absence factor-II. Detection of protein induced by vitamin K absence-II is considered to be a more specific test for vitamin K deficiency.[2]

We studied the vitamin K status in 21 severely disabled children and found 9 with hematologic and/or clinical evidence of vitamin K deficiency. It is important to consider this serious complication in severely disabled children.

PATIENTS AND METHOD

Patients

We studied 21 severely disabled children, retrospectively, treated at the Department of Pediatrics of Niigata City General Hospital from September 2001 to August 2002. They were aged from 10 months to 20 years, and 12 were boys and 9 were girls. The patients were divided into two groups: group A, patients with vitamin K deficiency (9 patients; 4 males and 5 females), and group B, patients without vitamin K deficiency (12 patients; 8 males and 4 females). In group A, none of the patients were thought to have vitamin K deficiency until the diagnosis was made. After the vitamin K deficiency was discovered, all patients received vitamin K supplementation either orally or intravenously. Case 5 has already been

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Table 1. Summary of the Clinical Features in Nine Severely Disabled Children With Vitamin K Deficiency

Case	Age/ Sex	BW (kg)	Diag- nosis	Drug	Nutrition	Calorie (kcal/kg)	GS	TT	GER	Bleeding Tendency	Pyrexia	Hepatic Dys- function	Antibiotics
1	1 yr, 7 mo/F	9	AE	VPA, DZP	Elental	80	+	−	+	+ 3	+	+	CMNX 3 d
2	1 yr, 5 mo/M	8	CP	VPA, PHT	Ensure	68	−	−	+	−	+	−	FMOX 3 d
3	15 yr/M	20	AE	VPA, DZP	Elental	50	+	+	+	+ 1	+	−	CMNX 4 d
4	13 yr/M	18	CP	PB, PHT	Twinline	45	−	−	+	+ 1	+	−	CMNX 2 d
5	1 yr, 10 mo/F	7	CP	VPA, CZP	Elental P	50	+	+	+	+ 1, 2	+	−	
6	2 yr, 8 mo/M	15	CP	VPA, NZP	Ensure	50	+	+	+	+ 1, 3	+	−	
7	10 mo/F	4	CP	PB	Elental P	40	−	−	+	−	−	+	
8	10 yr/F	25	HE	VPA, CZP, PHT	Elental	40	−	−	+	+ 1	−	+	
9	2 yr, 6 mo/F	7	CP	ZNS, BRM	Elental P	50	+	−	+	+ 1	−	−	

AE = anoxic encephalopathy; BRM = bromide; BW = body weight; CP = cerebral palsy; CMNX = cefminox sodium; CZP = clonazepam; DZP = diazepam; FMOX = flomoxef sodium; G.S = gastrostomy; GER = gastroesophageal reflux; HE = herpes encephalitis; NZP = nitrazepam; PB = phenobarbital; PHT = phenytoin; VPA = valproic acid.; ZNS = zonisamide.
1 = gastric bleeding, 2 = intratracheal bleeding, 3 = oozing from the granulation tissues around the gastrostomy and/or tracheostomy tube.

reported elsewhere.[3] Informed consent to use their data in this study was obtained from the patients' parents.

Methods

Data were gathered from the medical records of the patients. Their clinical backgrounds and clinical features were examined. Laboratory parameters, including glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, total protein, and hemoglobin, were measured. To assess the nutritional condition, body weight, calorie intake, total protein level, and hemoglobin level were compared between the two groups. Also, protein induced by vitamin K absence-II, thrombotest, and prothrombin time value were examined as indicators of vitamin K deficiency. Vitamin K deficiency is defined as an increase in the protein induced by vitamin K absence-II value (> 130 mAU/mL), a decrease in the thrombotest value, and prolongation of the prothrombin time, which become normalized after the administration of vitamin K, and/or an accompanying bleeding tendency.

Data Analysis

For comparison of age, body weight, calorie intake, total protein level, and hemoglobin level between the two groups, statistical analysis was performed using the *t*-test. Factors affecting the vitamin K status, such as use of antibiotics, infection, hepatic dysfunction, enteral feeding, elemental nutrition, and gastrostomy, were compared between the two groups using the chi-square test. $P < .05$ 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.

RESULTS

Clinical Features

The clinical background features in group A are summarized in Table 1. In group A, the nine patients were aged from 10 months to 15 years. Four were boys and five were girls. Six of them had cerebral palsy and mental retardation as sequelae of perinatal or prenatal brain insults, two sequelae of anoxic encephalopathy owing to drowning, and one sequelae of herpes encephalitis. All were severely disabled and in a bedridden state. All patients had various types of epilepsy and were administered antiepilepsy drugs, including phenytoin and phenobarbital, which are hepatic enzyme–inducing antiepilepsy drugs. All were fed by means of enteral nutrition; six were given an elemental diet (Elental, Elental P) and three were given a nonelemental diet (Ensure Liquid,Twinline). Five were fed by means of a gastrostomy tube and four by means of a nasogastric tube. All nine patients were diagnosed as having gastroesophageal reflux based on clinical symptoms and the results of lower esophageal 24-hour pH monitoring. Four underwent tracheotomy. A bleeding tendency, such as gastrointestinal bleeding, intratracheal bleeding, and oozing from granulation tissue around the tracheotomy or gastrostomy tube, was observed in seven patients. Pyrexia associated with an infectious disease was observed in six patients. Antibiotics were administered intravenously for 2 to 4 days in four (three received cefminox sodium and one flomoxef sodium) of the six patients with pyrexia. Hepatic dysfunction, such as elevated glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase values, was seen in three patients.

In group B, six of the children had cerebral palsy and mental retardation as sequelae of perinatal brain insults, two had chromosomal abnormalities, two had sequelae of acute encephalitis, one had hydrocephalus, and one had a sequela of anoxic encephalopathy. Eight patients were fed by means of enteral nutrition, one of whom received elemental nutrition, and four could eat with support. Gastrostomy was performed in two patients. All patients had epilepsy and were treated with antiepilepsy drugs. None received antibiotics.

Laboratory Findings

The laboratory findings in group A are summarized in Table 2. The protein induced by vitamin K absence-II values were elevated from 611 to 103,000 (mAU/mL) in all patients before the adminis-

Table 2. Summary of Laboratory Findings in Nine Severely Disabled Children With Vitamin K Deficiency

Case	PIVKA (mAU/mL)	Thrombotest (%)	PT (sec)	GOT (IU)	GPT (IU)	TP (g/dL)	Hb (g/dL)	Vitamin K Supplement
1	9020	NA	19.6	68	91	5.7	11.0	
	327	40	NA	65	26	7.3	11.9	After PO
2	1920	NA	NA	42	19	5.6	9.0	
	146	123	13.0	37	15	6.2	9.0	After PO
3	NA	NA	118.0	35	8	8.4	14.7	
	NA	56	13.0	35	12	8.2	15.7	After IV
4	1270	NA	12.3	36	23	6.6	13.5	
	NA	NA	12.3	33	29	6.7	12.3	After IV
5	103,000	< 5	68.0	25	7	6.6	9.3	
	NA	69	12.8	20	6	6.0	8.3	After IV
6	1060	65	NA	23	12	7.0	15.8	
	110	69	13.7	16	7	7.0	12.8	After PO
7	2050	51	14.6	184	484	5.9	9.8	
	145	81	13.0	36	35	7.0	10.0	After IV
8	4640	51	NA	169	141	7.7	14.6	
	59	46	12.9	92	70	7.2	13.0	After PO
9	611	41	13.7	39	17	6.8	12.1	
	21	45	NA	39	37	6.4	11.0	After PO
NR	< 130	> 70	< 13.8	11–31	7–42	6.6–8.0	10.9–14.3	

The lower lane for each case shows the laboratory data after the administration of vitamin K.
PIVKA = protein induced by vitamin K absence; GOT = glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase; Hb = hemoglobin; IV = intravenous administration; NA = not available; NR = normal range; PO = oral administration; PT = prothrombin time; TP = total protein.

tration of vitamin K. The thrombotest value was decreased in six patients to less than 70%, and the prothrombin time was prolonged in four cases. Although the serum levels of glutamic-oxaloacetic transaminase and/or glutamic-pyruvic transaminase were elevated in three patients, the etiology of hepatic dysfunction remained unclear because there was no evidence of viral infection, metabolic disturbance, or toxins. Four were treated with intravenous administration of vitamin K_2 and five with oral administration of vitamin K_2. In all patients, following the administration of vitamin K, the bleeding diasthesis disappeared completely and the protein induced by vitamin K absence-II values decreased markedly, with the abnormal thrombotest and/or prothrombin time values also improving. In case 3, protein induced by vitamin K absence-II was not measured; however, marked prolongation of the prothrombin time, which became normalized after the administration of vitamin K, could confirm the vitamin K deficiency. In cases 4 and 5, protein induced by vitamin K absence-II was not measured after the administration of vitamin K. In case 5, the thrombotest and prothrombin time values normalized after the vitamin K administration. In case 4, although the prothrombin time did not change after the vitamin K administration, the bleeding tendency disappeared quickly.

Statistical Analysis

Table 3 presents a summary of the nutritional factors in the two groups. The patients in the two groups were similar in average age ($P > .05$). Nutritional factors, such as total protein level, hemoglobin level, and calorie intake, were not significantly different between the two groups (see Table 3). The patients in group A exhibited significantly high incidences of factors such as use of antibiotics, infection, and elemental nutrition (Table 4) ($P < .05$). However, factors such as hepatic dysfunction, enteral feeding, and gastrostomy exhibited no significance as to the development of vitamin K deficiency (see Table 4).

DISCUSSION

Vitamin K is a cofactor for conversion of the glutamic acid residues of specific proteins into γ-carboxyglutamic acid residues.[2] Vitamin K deficiency causes impairment of the clotting factors, resulting in a bleeding tendency to various degrees. Vitamin K is also a carboxylation cofactor in various tissues, such as bone, cartilage, placenta, lung, and testicle, and is known as an important factor for bone mineralization and the prevention of bone fractures in severely disabled children.[4,5] Biochemically, vitamin K deficiency results in the appearance of abnormal prothrombin, deficient in γ-carboxyglutamic acid, in the blood. This abnormal prothrombin is named "protein induced by vitamin K absence for factor II".[2] Vitamin K deficiency is usually assessed by determining whether there is a prolongation of the prothrombin time, decreases in thrombotest values, and an increase in the protein induced by vitamin K absence-II value. It is known that prothrombin time is prolonged and protein induced by vitamin K absence-II value increases physiologically in the neonatal period. However, our study did not include neonates. The diagnosis of vitamin K deficiency must be confirmed by demonstrating that the protein induced by vitamin K absence level decreases on the administration of vitamin K. The protein induced by vitamin K absence-II level appears to be more sensitive than other indicators. Thus, mild vitamin K deficiency may be identified in patients with detectable protein induced by vitamin K absence-II (> 130 mAU/mL) but with a normal prothrombin time. In our case 4, the prothrombin time was not impaired, and in cases 5, 8, and 9, the prothrombin time or thrombotest values did not change after the administration of vitamin K. Protein induced by vitamin K absence-II has also been used as a marker for hepatic carcinomas in adults; however,

Table 3. Comparison of the Nutritional Factors Between the Two Groups

	Number	*Age (yr)*	*Body Weight (kg)*	*Calories (kcal/kg)*	*TP (g/dL)*	*Hb (g/dL)*
A	9	5.44 ± 5.58	12.55 ± 7.19	52.55 ± 13.18	6.70 ± 0.92	12.20 ± 2.56
B	12	6.63 ± 5.29	13.66 ± 5.97	55.37 ± 10.80	6.88 ± 0.61	13.40 ± 1.35
P		NS	NS	NS	NS	NS

TP = total protein; Hb = hemoglobin; NS = not significant.

responsiveness to vitamin K therapy does not indicate liver dysfunction.

Factors contributing to vitamin K deficiency include malnutrition, malabsorption owing to a chronic gastrointesitinal disorder,[6] suppression of intestinal bacterial flora owing to enteral nutrition[7,8] and antibiotics therapy,[9,10] and hepatic dysfunction. In severely disabled children fed by means of enteral nutrition, there are many factors influencing vitamin K deficiency in their daily life. In this study, all nine patients with vitamin K deficiency received enteral nutrition and six received elemental nutrition. Thus, elemental nutrition might exhibit some relationship with vitamin K deficiency. However, it is unknown whether an elemental diet itself influences the vitamin K status or whether a pathologic condition needing elemental nutrition has something to do with vitamin K deficiency. The dietary requirement of vitamin K for children and adults is usually stated to be more than 1 μg/kg body weight per day.[11] All of our patients with vitamin K deficiency received at least 2.5 μg/kg body weight via enteral nutrition. Nutritional factors did not differ between groups A and B. However, in some patients, the total protein and hemoglobin levels were under the normal ranges, which might indicate subclinical malnutrition. A long-term effect of enteral and/or elemental nutrition on vitamin K metabolism is not well recognized, and there are no data regarding vitamin K requirements in severely disabled children. Additional vitamin K supplementation may be required for severely disabled children, especially ones receiving enteral nutrition.

Severely disabled children sometimes need an elemental diet because of some absorption difficulty in the gut. It is known that enteral nutrition induces colonic and intestinal mucosal atrophy[12] and a gastrointestinal microflora change[7] as adverse effects. Although the pathologic findings in the gastrointestinal tracts of severely disabled children after a long-term elemental diet were not well known, Iai and Yamada[13] reported intestinal mucosal atrophy in a severely disabled person after 25 years of enteral nutrition. This finding suggests that intestinal atrophy occurs in severely disabled children on prolonged enteral nutrition. This intestinal mucosal atrophy may be one reason for vitamin K deficiency owing to malabsorption of nutrients. Kakihara[7] reported that prolonged elemental nutrition in rats caused a change in the intestinal microflora, which induced vitamin K deficiency. Vitamin K is synthesized by intestinal bacteria, and a deficiency of it develops in compromised patients. Vitamin K deficiency does not develop in healthy children receiving a normal diet. These gastrointestinal changes in severely disabled children may cause malabsorption of vitamin K and decreased production of vitamin K by microflora in the gut, which result in vitamin K deficiency.

In addition to these conditions, vitamin K deficiency may be aggravated by concomitant administration of several broad-spectrum antibiotics[9,10] and infection. It has been reported that the use of antibiotics containing an *N*-methylthiotetrazole side chain is associated with an increased incidence of hypoprothrombinemia through the direct effect of *N*-methylthiotetrazole on the vitamin K–dependent γ-carboxylation of clotting factors.[9,10] In the present study, four patients received antibiotic therapy when they developed vitamin K deficiency. Although cefminox sodium has *N*-methylthiotetrazole residues, this theory remains controversial because Allison et al[14] reported that there was no evidence that *N*-methylthiotetrazole-containing antibiotics had a greater effect on vitamin K–dependent reactions than other broad-spectrum antibiotics. Pyrexia and infections themselves induce hyperuse of some vitamins and necessitate higher doses of vitamins than usual. On the other hand, hospitalized patients with minimal oral intake and ones on antibiotics have been noted to develop vitamin K deficiency.[15,16] Severely disabled, bedridden children are in a situation similar to that of chronic hospitalized patients. Presumably, such patients require more vitamin K than usual, and especially for ones with malabsorption and ones receiving antibiotics, the requirements of some nutrients including vitamin K may be greater. However, it is unknown whether disability itself is a factor causing vitamin K deficiency because we have no control patients with severe illness without disability.

Davis et al[17] have shown significantly raised protein induced by vitamin K absence-II levels in a group of adult epileptic patients undergoing chronic anticonvulsant therapy,

Table 4. Factors Affecting Vitamin K Deficiency

	Number	*Antibiotics*	*Infection*	*Hepatic Dysfunction*	*Enteral Feeding*	*Elemental Nutrition*	*Gastrostomy*
A	9	4/9	6/9	3/9	9/9	6/9	5/9
B	12	0/12	0/12	0/12	8/12	1/12	2/12
P		< .05	< .01	NS	NS	< .05	NS

NS = not significant.

and there was no correlation between the protein induced by vitamin K absence-II concentration and the particular anticonvulsants being taken. Keith et al[18] reported that the urine-carboxylglutamic acid level decreased in 41% of epileptic patients taking phenytoin. However, Origuchi et al[19] reported that no elevation of protein induced by vitamin K absence-II was recognized in epileptic patients and thus ruled out their conclusion. It is also known that maternal hepatic enzyme–inducing antiepilepsy drugs such as phenobarbital, phenytoin, and carbamazepine increase the risk of neonatal bleeding owing to alterations in vitamin K metabolism in the neonate. However, Kaaja et al[20] reported that their data do not support the hypothesis that maternal enzyme–inducing antiepilepsy drugs increase the risk of bleeding in the offspring. In our three patients receiving phenytoin or phenobarbital, their influence on the vitamin K status remains unknown because our patients were not neonates.

Kumode et al[1] reported that, based on the data obtained through a questionnaire sent to 145 institutes for the severely handicapped in Japan, vitamin K deficiency was recognized in only 5 cases, and in these institutes, it was reported that 14.8% of the patients died owing to a hemorrhagic tendency of the gastrointestinal tracts and trachea. Our results also indicated that vitamin K deficiency is not common in severely disabled children with enteral nutrition and concomitant treatment with antibiotics. However, most cases were incorrectly diagnosed as having other gastrointestinal complications. When the bleeding in such patients is resistant to the usual therapy, vitamin K status should be examined because vitamin K supplementation could quickly stop the bleeding tendency. We must pay attention to vitamin K deficiency in severely disabled children.

References

1. Kumode M, Mekata Y, Hujita Y, Shimada M: Problem of long-term enteral nutrition on the severely disabled [in Japanese]. *J Severe Motor Intellect Disabil* 1994;19:53–57.
2. Shearer MJ: Vitamin K. *Lancet* 1995;345:229–234.
3. Yoshikawa H: Severely disabled children with vitamin K deficiency due to unknown origin. *J Severe Motor Intellect Disabil* 2002;27:157–159.
4. Binkley NC, Suttie JW: Vitamin K nutrition and osteoporosis. *J Nutr* 1995;125:1812–1821.
5. Tanaka Y, Shibata R: Effects of vitamin K2 administration in the patients with severely motor and intellectual disabilities: Assessment of bone metabolic marker and bone mineral density. *No To Hattatsu* 2000;32:491–496.
6. Krasinski SD, Russel RM, Furie BC, et al: The prevalence of vitamin K deficiency in chronic gastrointestinal disorders. *Am J Clin Nutr* 1985;41:639–643.
7. Kakihara M: Effects of a long-term elemental diet on gastrointestinal microflora in rats. *Nippon Shoukakigeka Gakkai Zasshi* 1987;20:1076–1086.
8. Bounous G, Devroede GL: Effects of an elemental diet on human fecal flora. *Gastroenterology* 1974;66:210–214.
9. Uchida K, Ishigami T, Komeo T: Effects of latamoxef and methyltetrazolethiol on gamma-glutamylcarboxylase activity. *Jpn J Pharmacol* 1984;35:330–333.
10. Bechthold H, Andrassy K, Jahnchen E, et al: Evidence for impaired hepatic vitamin K1 metabolism in patients treated with N-methylthiotetrazole cephalosporins. *Thromb Haemost* 1984;51:358–361.
11. National Research Council, Food and Nutrition Board. Fat-soluble vitamins, in *Recommended Dietary Allowances*, 10th ed. Washington, DC, National Academy Press, 1989, 78–114.
12. Janne P, Carpentier Y, Willems G: Colonic mucosal atrophy induced by a liquid elemental diet in rats. *Am J Dig Dis* 1977;22:808–812.
13. Iai M, Yamada M: Tube feeding for children with severe motor and intellectual disabilities. *Nippon Rinshou* 2001;59:819–821.
14. Allison PM, Mummah-Schendel LL, Kindberg CG, et al: Effects of a vitamin K-deficient diet and antibiotics in normal human volunteers. *J Lab Clin Med* 1987;110:180–188.
15. Jatoi A, Lennon C, O'Brien M, et al: Protein-calorie malnutrition does not predict subtle vitamin K depletion in hospitalized patients. *Eur J Clin Nutr* 1988;52:934–937.
16. Alperin JB: Coagulopathy caused by vitamin K deficiency in critically ill, hospitalized patients. *JAMA* 1987;258:1916–1919.
17. Davis VA, Rothberg AD, Argent AC, et al: Precursor prothrombin status in patients receiving anticonvulsant drugs. *Lancet* 1986;i:126–128.
18. Keith DA, Gundberg CM, Gallop PM: Phenytoin therapy and hemorrhagic disease. *J Pediatr* 1980;96:501.
19. Origuchi Y, Motohara K, Endo F, Matsuda I: Plasma PIVKA− levels in epileptic patients. *Brain Dev* 1990;12:451.
20. Kaaja E, Kaaja R, Matila R, Hiilesmaa V: Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. *Neurology* 2002;58:549–553.

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ORIGINAL ARTICLE

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Renal involvement in children with influenza A virus infection

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Abstract Renal involvement in influenza A virus infection has been rarely reported. To define the clinical characteristics and the factors contributing to the development of renal involvement in influenza A virus infection, we reviewed the clinical characteristics, laboratory data, pediatric risk of mortality (PRISM) score, and the number of systemic inflammatory response syndrome (SIRS) criteria and dysfunctional organs in 45 hospitalized children with influenza A virus infection. Eleven (24.4%) patients had renal involvement. All patients with renal involvement suffered from sepsis and multiple organ dysfunction syndrome (MODS) and 5 developed acute renal failure (ARF). The incidences of dehydration, hypotension, disseminated intravascular coagulation (DIC), and rhabdomyolysis were significantly higher in patients with renal involvement. PRISM scores, the numbers of SIRS criteria and dysfunctional organs, and mortality rate were also higher in patients with renal involvement. Influenza A RNA was absent in the renal tissues of 3 patients with ARF. These results suggested that renal involvement in influenza A virus infection occurred in patients with sepsis and MODS; dehydration, hypotension, DIC, and rhabdomyolysis were factors contributing to its development; direct viral injury to the kidney did not seem to occur in influenza A virus infection.

Keywords Renal injury · Kidney disease · Acute renal failure · Complications · Multiple organ dysfunction syndrome · Systemic inflammatory response syndrome

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Introduction

Influenza A virus infection is a common cause of acute respiratory illness in children [1, 2]. While most influenza A virus infections are self-limited, infants and young children, even without chronic or serious medical conditions, are at increased risk for hospitalization for illnesses attributable to influenza [2, 3], and some die from their complications [4]. There are various complications of influenza A virus infection in the pulmonary (primary viral pneumonia, secondary bacterial pneumonia, croup syndrome, and acute exacerbation of bronchial asthma attack), neurological (febrile convulsions, Reye syndrome, encephalitis, encephalopathy, transverse myelopathy, and Guillain-Barré syndrome), cardiac (myocarditis and pericarditis), and muscular (myosytis) systems [1, 4]. Recently, Yuen et al. [5] reported that 12 patients with human infection with an avian influenza A virus (H5N1) in Hong Kong, 1997, had severe disease and a high rate of complications, and 3 developed acute renal failure (ARF). However, clinical characteristics of patients with human influenza A virus infection and renal involvement remain unclear. ARF due to rhabdomyolysis has sometimes been reported as a renal complication of influenza A virus infection [6, 7, 8, 9, 10, 11, 12, 13]. Other renal involvement has rarely been described [6, 14, 15, 16, 17, 18, 19]. Most patients had severe illness and multiple organ dysfunction syndrome (MODS) [20, 21, 22]. Therefore, the severity of the patient's illness may influence the development of renal injury in influenza A virus infection.

The aims of this study were to define the clinical characteristics of renal involvement in hospitalized patients with influenza A infection and to determine the factors necessary for its development.

Patients and methods

Medical records of all 45 patients with influenza A virus infection admitted to the Department of Pediatrics, Niigata City General

Hospital between 1997 and 2000 were retrospectively reviewed. Charts were reviewed for clinical characteristics including patient age, sex, complications, outcome, and presence of dehydration, hypotension, disseminated intravascular coagulation (DIC), rhabdomyolysis at admission, non-steroidal anti-inflammatory drugs (NSAIDs) usage before admission, and renal involvement during hospitalization. Laboratory data at admission included blood urea nitrogen (BUN) levels, serum concentrations of creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH), urinary protein, and urinary red blood cell counts (cells/high-power field). The pediatric risk of mortality (PRISM) scores [23], the number of systemic inflammatory response syndrome (SIRS) criteria [20], and the number of dysfunctional organs [20] were also noted. The laboratory data, PRISM scores, and the numbers of SIRS criteria and dysfunctional organs were recorded at the time of admission.

Influenza A virus infection was confirmed by viral isolation from nasopharyngeal swabs, the detection of virus RNA in nasopharyngeal swabs with the reverse transcription-polymerase chain reaction (RT-PCR) technique using subtype-specific primers for the influenza A hemagglutinin gene [24], or serological tests (a fourfold or greater rise in hemagglutinin inhibition titers against influenza A virus during the acute and convalescent phases) [4].

Renal involvement was defined by rising levels of serum creatinine more than the normal range for age (mean+2 SD) [25] and/or presence of both hematuria (>10 cells/high-power field) and proteinuria (>10 mg/dl). ARF was defined using the following criteria: an abrupt drop of renal function without known underlying kidney disease, characterized by oliguria, less than 0.5 ml/kg per hour, and confirmed by rising levels of serum creatinine to double that of normal for age [13, 25, 26]. Dehydration was defined by weight loss >5% and/or the presence of clinical findings of dehydration, such as dry mucous membrane, decreased skin turgor, sunken anterior fontanelle, tachycardia, or hemoconcentration (hematocrit >50%), all resolving with fluid administration [13]. Hypotension was defined by blood pressure less than the 3rd percentile for age [20, 27]. SIRS, organ dysfunction other than the renal system, and MODS were defined by the criteria of Proulx et al. [20]. Encephalopathy was defined as an upper respiratory tract infection or fever followed by symptoms in the central nervous system that could not be explained by other identifiable causes [28, 29].

We summarized clinical characteristics of patients with renal involvement, and then compared clinical characteristics, laboratory data, PRISM scores, and the numbers of SIRS criteria and dysfunctional organs between patients with and without renal involvement.

Descriptive statistics are presented as median and range. Analyses for the association of categorical variables were performed using Fisher's exact test. A comparison between two groups was performed using the Mann-Whitney U test. All data were analyzed using StatView 5.0 (SAS Institute, Cary, N.C., USA). $P<0.05$ was considered significant.

Results

Forty-five patients with influenza A infection (26 males and 19 females, aged 1 month to 14 years) were included. No patient had underlying kidney disease. Complications of influenza A virus infection were as follows: exacerbation of bronchial asthma attack 15; influenza A virus-associated encephalopathy 14; febrile convulsions 7; secondary bacterial pneumonia 3; enterocolitis 3; croup syndrome 1; myocarditis 1; and hemolytic uremic syndrome (HUS) due to influenza A 1. Of 45 patients, 4 (8.8%) died.

Eleven patients (24.4%) had renal involvement. Their clinical characteristics are summarized in Table 1. Patients 1 [16] and 5 [10] have been reported previously. Ten patients had both hematuria and proteinuria. Urinalysis could not be performed in patient 2 because the patient died before urinary voiding. Seven patients had rising levels of serum creatinine more than normal range for age. As complications of influenza A infection, encephalopathy occurred in 9 patients, croup syndrome in 1, and HUS in 1. Dehydration was present in 7 patients (63.6%), hypotension in 5 (45.4%), DIC in 7 (63.6%), and rhabdomyolysis in 3 (27.3%). Five patients (45.4%) used NSAIDs before admission compared with 7 patients (20.6%) without renal involvement. All patients fulfilled the criteria for SIRS (sepsis) and MODS. Four patients died.

Five patients developed ARF, which was caused by hemodynamic disturbance due to MODS in 3 patients, rhabdomyolysis in 1, and HUS in 1. All patients with ARF exhibited oliguria, and 2 underwent hemodialysis. Two patients recovered completely from ARF and survived. The other 3 patients with ARF died from MODS. Renal histological study, obtained by biopsy or necropsy from 3 patients, showed acute tubular necrosis (patient 1), fibrin thrombi in the renal arterioles probably due to DIC (patient 3), or findings compatible with HUS (patient 5). Subtype-specific hemagglutinin of influenza A RNA, examined by RT-PCR, was absent in the renal tissues taken from these patients [16].

Dehydration, hypotension, DIC, and rhabdomyolysis at admission were significantly more common in patients

Table 1 Clinical details of patients with renal involvement (*ARF* acute renal failure, *DIC* disseminated intravascular coagulation syndrome)

Patient no.	Age years/ sex	Complication	Dehydration	Hypotension	DIC	Rhabdomyolysis	ARF	Outcome
1	5/M	Encephalopathy	+	+	+	+	+	Survived
2	5/F	Encephalopathy	+	+	+	−	+	Died
3	2/M	Encephalopathy	+	−	+	−	+	Died
4	3/F	Encephalopathy	−	−	+	−	+	Died
5	3/F	Hemolytic uremic syndrome	+	+	−	−	+	Survived
6	2/M	Encephalopathy	+	+	+	−	−	Survived
7	4/M	Encephalopathy	−	−	+	−	−	Survived
8	3/F	Encephalopathy	+	+	+	+	−	Died
9	1/M	Encephalopathy	−	−	−	−	−	Survived
10	2/M	Encephalopathy	+	−	−	+	−	Survived
11	1/M	Croup syndrome	−	−	−	−	−	Survived

Table 2 Comparison of clinical variables between patients with and without renal involvement (*NSAIDs* non-steroidal anti-inflammatory drugs, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *BUN* blood urea nitrogen, *SIRS* systemic inflammatory response syndrome)

Variable	Patients with renal involvement (n=11)	Patients without renal involvement (n=34)	P value
Age (years)	3.3 (1.6–5.8)	2.7 (0.1–14.3)	0.8492
Sex (M/F)	7/4	19/15	0.7363
Influenza A subtype (H1N1/H3N2)	2/9	8/26	>0.9999
NSAIDs usage	5	7	0.1306
Dehydration	7	5	0.0035*
Hypotension	5	1	0.0020*
DIC	7	1	<0.0001*
Rhabdomyolysis	3	0	0.0116*
Death	4	0	0.0022*
Serum AST (IU/l)	409 (116–5,534)	37.5 (16–1,400)	<0.0001*
Serum ALT (IU/l)	194 (19–4,080)	14 (5–1,117)	<0.0001*
Serum LDH (IU/l)	2,146 (608–10,194)	531 (321–3,630)	<0.0001*
BUN (mg/dl)	36.0 (10.7–83.8)	10.3 (2.4–31.9)	<0.0001*
Serum creatinine (mg/dl)	1.6 (0.4–3.6)	0.3 (0.2–0.9)	<0.0001*
PRISM score	21 (12–40)	0 (0–13)	<0.0001*
No. of SIRS criteria	3 (2–4)	1 (1–3)	<0.0001*
No. of dysfunctional organs	3 (2–6)	0(0–2)	<0.0001*

*P values represent significant differences

with renal involvement (n=11) than in patients without renal involvement (n=34) (Table 2). PRISM scores, the number of SIRS criteria, and dysfunctional organs at admission were significantly higher in patients with renal involvement. The mortality rate was also significantly higher in patients with renal involvement. BUN levels and serum concentrations of creatinine, AST, ALT, and LDH at admission were significantly higher in patients with renal involvement. There were no differences in age, sex ratio, influenza A subtypes, and NSAIDs usage between patients with and without renal involvement.

Discussion

Since renal involvement in patients with influenza A virus infection is uncommon, being reported mostly as single cases or a small series of patients, the clinical characteristics of renal injury in patients with influenza A virus infection remain unclear. In our study, 24.4% of hospitalized patients with influenza A virus infection had some findings of renal injury. Because most patients with influenza A virus infection have no complications and do not need hospitalization, the actual incidence of renal injury in patients with influenza A virus infection is lower than in our study. In addition, since our hospital is one of the central hospitals for emergency and critical care in our prefecture, many severely ill patients were transferred to our hospital from other local hospitals. This may explain the unexpectedly high rate of renal involvement in patients with influenza A virus infection in the present study.

While pathogenic mechanisms for the development of renal injury in influenza A virus infection are not completely understood, four potential causes are postulated: rhabdomyolysis, direct viral injury to the kidney, renal hypoperfusion due to sepsis, and DIC [6, 17]. Among these causes, rhabdomyolysis has been most frequently reported [6, 7, 8, 9, 10, 11, 12, 13], and is a definitive cause of renal injury in influenza A infection. Rhabdomyolysis can induce renal injury due to renal vasoconstriction, tubular cast formation, and direct heme protein-induced cytotoxicity [30]. In our study, 3 of 11 (27.3%) patients with renal involvement had rhabdomyolysis; 1 of these 3 patients developed ARF [10]. In addition, rhabdomyolysis was more common in patients with renal involvement than in patients without renal involvement.

Direct viral injury to the kidney does not seem to occur in influenza A virus infection. There have been no reports of influenza A virus or its RNA in renal tissues of patients with influenza A infection. We also did not detect influenza A virus RNA in renal tissues of 3 patients with influenza A virus infection and renal involvement.

Sepsis is one of the main causes of ARF [31]. In sepsis, several mechanisms of organ failure have been proposed, including immunological dissonance, tissue hypoxia, and reperfusion injury [32]. Renal tissue hypoxia can be caused by hypovolemia due to dehydration or hypotension resulting from myocardial dysfunction or hypovolemia [31, 32].

Some patients with renal involvement of influenza A virus infection have suffered from DIC [6, 14, 15, 16, 17]. DIC occurs frequently in patients with sepsis, and is associated with organ dysfunction [33]. Proinflammatory cytokines, particularly tumor necrosis factor-α and interleukin-6, released early in the course of sepsis stimulate a procoagulant state that causes development of intravascular fibrin deposition, which results in DIC and organ dysfunction, including kidney dysfunction [15, 33]. These findings suggest that rhabdomyolysis, renal hypoperfusion (dehydration or hypotension), and DIC could be contributory factors in the development of renal involvement in influenza A virus infection.

Most reported patients with renal involvement in influenza A virus infection had severe illness and MODS [20, 21, 22]. Shenouda and Hatch [6] reported four patients with ARF due to influenza A virus infection, and all four suffered from MODS. Davison et al. [14] described two patients with DIC and influenza A virus infection; both had MODS and one developed ARF. Whitaker et al. [15] reported six patients with ARF and MODS caused by influenza A infection. We recently reported a patient with HUS associated with influenza A virus infection, with MODS and ARF [16]. West and Brunskill [17] reported a patient with influenza A infection and ARF caused by hemodynamic disturbance due to MODS. ARF is thought to be a part of MODS in septic patients [31, 32]. These findings suggest that MODS is an important underlying condition for the development of renal involvement in influenza A virus infection.

The present study showed that all patients with renal involvement fulfilled SIRS (sepsis) and MODS criteria. The incidences of dehydration, hypotension, DIC, and rhabdomyolysis at the time of admission were significantly higher in patients with renal involvement than in patients without renal involvement. PRISM scores, the numbers of SIRS criteria and dysfunctional organs at the time of admission, and the mortality rate were also significantly higher in patients with renal involvement than in patients without renal involvement. Subtype-specific hemagglutinin of influenza A virus RNA was absent in the renal tissues of 3 patients with ARF. These findings indicated that renal involvement in influenza A virus infection occurred in patients with sepsis and MODS; dehydration, hypotension, DIC, and rhabdomyolysis were the factors contributing to its development; direct viral injury to the kidney does not seem to occur in influenza A virus infection.

References

1. Cox NJ, Subbarao K (1999) Influenza. Lancet 354:1277–1282
2. Neuzil KM, Mellen BG, Wright PF, Mitchel Jr EF, Griffin MR (2000) The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 342:225–231
3. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, Black S, Shinefield H, Fukuda K (2000) Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 342:232–239
4. Treanor JJ (2000) Influenza virus. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas and Bennett's principles and practice of infectious diseases, 5th edn. Churchill Livingstone, Philadelphia, pp 1823–1849
5. Yuen KY, Chan PKS, Peiris M, Tsang DNC, Que TL, Shortridge KF, Cheung PT, To WK, Ho ETF, Sung R, Cheng AFB (1998) Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 351:467–471
6. Shenouda A, Hatch FE (1976) Influenza A viral infection associated with acute renal failure. Am J Med 61:697–702
7. Cunningham E, Kohli R, Venuto RC (1979) Influenza-associated myoglobinuric renal failure. JAMA 242:2428–2429
8. Berry L, Braude S (1991) Influenza A infection with rhabdomyolysis and acute renal failure – a potentially fatal complication. Postgrad Med J 67:389–390
9. Dell KM, Schulman SL (1997) Rhabdomyolysis and acute renal failure in a child with influenza A infection. Pediatr Nephrol 11:363–365
10. Watanabe T, Oda Y (1998) Rhabdomyolysis and acute renal failure in acute necrotizing encephalopathy with influenza A. Pediatr Nephrol 12:85
11. Wakabayashi Y, Nakano T, Kikuno T, Ohwada T, Kikawada R (1994) Massive rhabdomyolysis associated with influenza A infection. Intern Med 33:450–453
12. Annerstedt M, Herlitz H, Mölne J, Oldfors A, Westberg G (1999) Rhabdomyolysis and acute renal failure associated with influenza virus type A. Scand J Urol Nephrol 33:260–264
13. Watanabe T (2001) Rhabdomyolysis and acute renal failure in children. Pediatr Nephrol 16:1072–1075
14. Davison AM, Thomson D, Robson JS (1973) Intravascular coagulation complicating influenza A virus infection. BMJ 1:654–655
15. Whitaker AN, Bunce I, Graeme ER (1974) Disseminated intravascular coagulation and acute renal failure in influenza A2 infection. Med J Aust 2:196–201
16. Watanabe T (2001) Hemolytic uremic syndrome associated with influenza A virus infection. Nephron 89:359–360
17. West SD, Brunskill NJ (2002) Complications associated with influenza infection. Postgrad Med J 78:107–108
18. Goodpasture EW (1919) The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci 158:863–870
19. Wilson CB, Smith RC (1972) Goodpasture's syndrome associated with influenza A2 virus infection. Ann Intern Med 76:91–94
20. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M (1996) Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest 109:1033–1037
21. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874
22. Watanabe T (1998) Serum ferritin levels in acute renal failure. Clin Nephrol 50:336
23. Pollack MM, Ruttimann UE, Getson PR (1988) Pediatric risk of mortality (PRISM) score. Crit Care Med 16:1110–1116
24. Yamada A, Imanishi J, Nakajima E, Nakajima S (1991) Detection of influenza viruses in throat swab by using polymerase chain reaction. Microbiol Immunol 35:259–265
25. Savory DJ (1990) Reference ranges for serum creatinine in infants, children and adolescents. Ann Clin Biochem 27:99–101
26. Williams DM, Sreedhar SS, Mickell JJ Chan JCM (2002) Acute kidney failure: a pediatric experience over 20 years. Arch Pediatr Adolesc Med 156:893–900
27. Lowrey GH (1973) Organ development. In: Lowrey GH (eds) Growth and development of children. Year Book Medical Publishers, Chicago, pp186–249
28. Fujimoto S, Kobayashi M, Uemura O, Iwasa M, Ando T, Katoh T, Nakamura C, Maki N, Togari H, Wada Y (1998) PCR on cerebrospinal fluid to show influenza-associated acute encephalopathy or encephalitis. Lancet 352:873–875
29. Ito Y, Ichiyama T, Kimura H, Shibata M, Ishiwada N, Kuroki H, Furukawa S, Morishima T (1999) Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. J Med Virol 58:420–425
30. Vanholder R, Sever MS, Erek E, Lameire N (2000) Rhabdomyolysis. J Am Soc Nephrol 11:1553–1561
31. Schor N (2002) Acute renal failure and the sepsis syndrome. Kidney Int 61:764–776
32. Breen D, Bihari D (1998) Acute renal failure as a part of multiple organ failure: the slippery slope of critical illness. Kidney Int 53:S25–S33
33. Levi M (2001) Pathogenesis and treatment of disseminated intravascular coagulation in the septic patient. J Crit Care 16: 167–177

Periodic Lateralized Epileptiform Discharges in Children

ABSTRACT

Thirteen children in whom electroencephalography revealed periodic lateralized epileptiform discharges in the acute phase of cerebral involvement were included in this study. Four were diagnosed as having influenza-associated encephalopathy, two nonherpetic limbic encephalitis, two theophylline-associated seizures, one *Mycoplasma pneumoniae* encephalitis, one acute encephalopathy, and one bacterial meningitis. All patients developed seizures; six developed hemiconvulsions. As to prognosis, two died, six had some neurologic sequelae, and five had no neurologic sequelae. Although periodic lateralized epileptiform discharges are not disease specific, the importance of these disorders had not been focused on as a cause of periodic lateralized epileptiform discharges. (*J Child Neurol* 2003;18:803–805).

Periodic lateralized epileptiform discharges, initially described by Chatrian et al in 1964,[1] are an electroencephalographic (EEG) entity consisting of lateralized or focal epileptiform discharges occurring in a periodic pattern. Periodic lateralized epileptiform discharges are often reflected synchronously over homologous areas in the contralateral hemisphere. These periodic discharges are a transient phenomenon and occur only during the acute phase, that is, when the patient is comatose. Although the underlying mechanisms related to the periodicity remain controversial, cortical isolation or lesions in the gray matter are suspected to be a critical mechanism. Periodic lateralized epileptiform discharges are not disease specific and occur in a variety of disorders, most often acute unilateral lesions such as cerebral hemorrhage, cerebral infarcts, tumors, infections such as herpes encephalitis, and various metabolic insults.

In children, the etiology of periodic lateralized epileptiform discharges has not been fully investigated. We report here 13 children showing periodic lateralized epileptiform discharges with various etiologies.

Patients and Method

Thirteen children in whom EEG revealed periodic discharges in the acute phase of cerebral involvements were seen in the Department of Pediatrics, Niigata City General Hospital, from 1996 to 2002, and they comprised the cases for this study. They were aged from 1 month to 12 years, and there were seven boys and six girls (Figure 1). Two were diagnosed as having non-

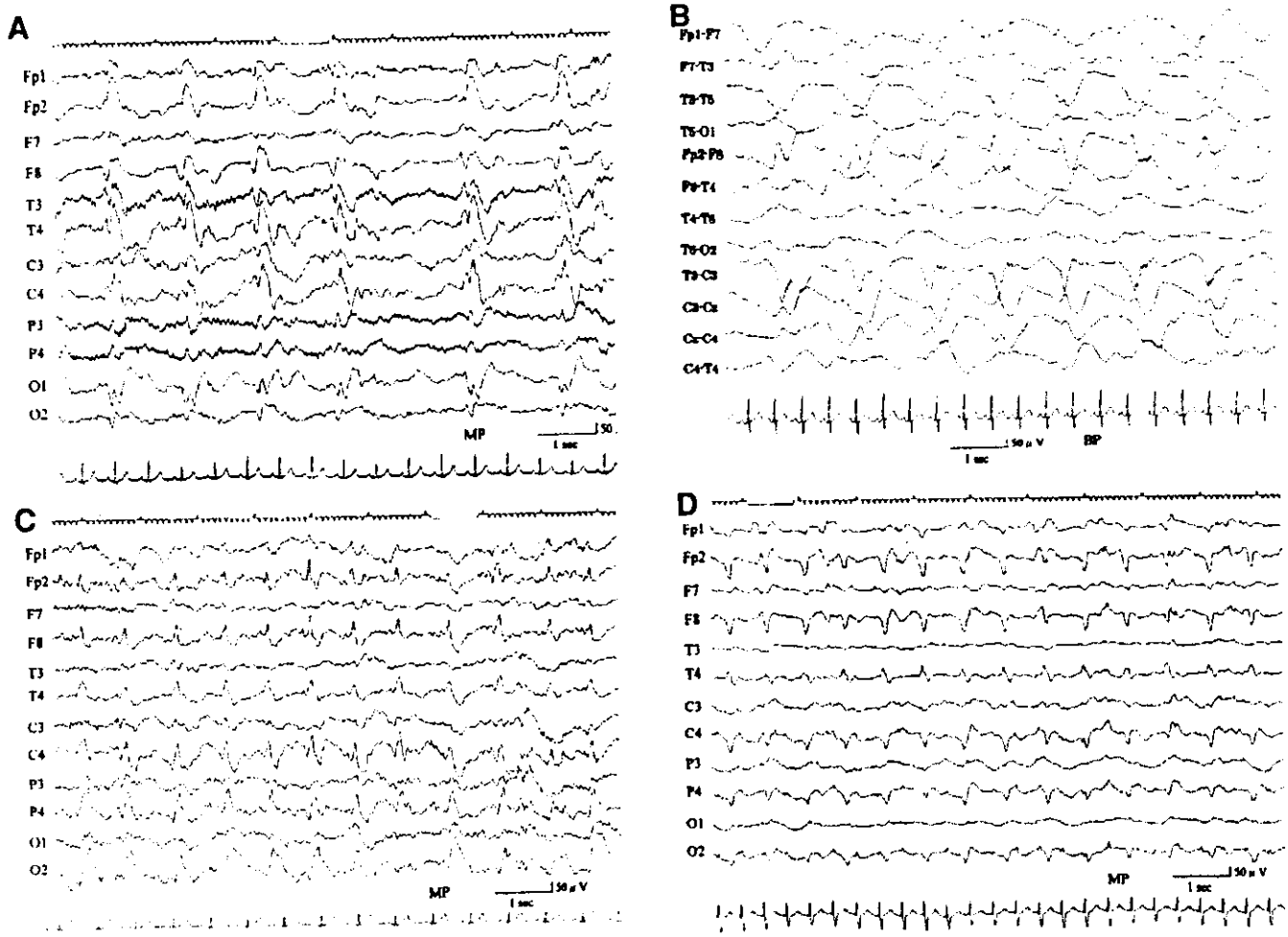

Figure 1. Electroencephalographic (EEG) findings of periodic lateralized epileptiform discharges. *A*, Case 2, limbic encephalitis: EEG revealed periodic lateralized epileptiform discharges, which were seen diffusely over the right hemisphere. The intervals of periodic discharges were approximately 1.0 to 2.0 seconds. *B*, Case 5, influenza encephalopathy: EEG showed repetitive epileptiform discharges in the right frontal area. *C*, Case 9, *Mycoplasma pneumoniae* encephalitis: EEG showed repetitive epileptiform discharges over the right hemisphere at one to two per second. *D*, Case 10, cerebral infarction: EEG demonstrated periodic lateralized epileptiform discharges over the right hemisphere.

Table 1. Clinical Summary of the 13 Patients Presenting Periodic Lateralized Epileptiform Discharges

	Age/ Sex	*Diagnosis*	*Consciousness Disturbance*	*Seizure*	*Neuroimaging*	*Periodic Discharge*	*Prognosis*
1	3 yr/F	Limbic encephalitis	Coma	GTC	Increased T_2 in bilateral temporal	Bilateral C	MR, TLE
2	4 yr/F	Limbic encephalitis	Semicoma	Lt hemiconvulsion	Increased T_2 in rt temporal	Rt C-temporal	NP
3	2 yr/F	Influenza encephalopathy	Coma	GTC	LDA in frontal	Lt temporal	MR, FLE
4	4 yr/M	Influenza encephalopathy	Semicoma	GTC	LDA in bilateral thalamus	Lt temporal	NP
5	2 yr/M	Influenza encephalopathy	Coma	Lt hemiconvulsion	Diffuse LDA	Lt temporal	MR
6	3 yr/F	Influenza encephalopathy	Coma	GTC	LDA in frontal	Rt C	MR, FLE
7	10 mo/M	Theophylline seizure	Coma	GTC	ND	Lt temporal	Death
8	4 yr/F	Theophylline seizure	Coma	GTC	NP	Lt temporal	NP
9	11 yr/M	*Mycoplasma* encephalitis	Coma	Lt hemiconvulsion	Increased T_2 in rt temporal	Rt temporal	NP
10	9 mo/F	Cerebral infarction	Semicoma	Rt hemiconvulsion	Diffuse LDA	Rt frontal	Rt hemiplegia, TLE
11	6 yr/M	Cerebral infarction	Coma	Rt hemiconvulsion	LDA in lt hemisphere	Lt frontal-C	Death
12	1 mo/M	Acute encephalopathy	Coma	GTC	Diffuse LDA	Rt C	MR
13	4 yr/M	Bacterial meningitis	Semicoma	Rt hemiconvulsion	NP	Bilateral frontal	NP

C = central; GTC = generalized tonic convulsion; FLE = frontal lobe epilepsy; LDA = low-density area; Lt = left; MR = mental retardation; ND = not done; NP = nothing particular; Rt = right; TLE = temporal lobe epilepsy.

herpetic limbic encephalitis (one was reported elsewhere[2]), four influenza-associated encephalopathy, two theophylline-associated seizures, one *Mycoplasma pneumoniae* encephalitis, one acute encephalopathy of unknown origin, and one bacterial meningitis. Influenza infection was confirmed by positive serologic test results and/or a positive antigen result with the polymerase chain reaction method. *Mycoplasma* infection was confirmed by an increased titer for anti-*Mycoplasma pneumoniae* antibodies and an increased cold hemagglutinin test result. Nonherpetic limbic encephalitis was identified according to the established criteria.[3] The serum concentration of theophylline in two patients with theophylline seizure was within normal limits. The children's clinical symptoms, clinical course, and laboratory findings, including electrophysiologic and neuroradiologic examinations, were studied.

Results

The consciousness level in the acute phase was severely disturbed when periodic lateralized epileptiform discharges were seen on EEG in all patients. All patients developed seizures. Seven developed generalized convulsion and six hemiconvulsions. Among the patients with hemiconvulsion, the seizure side was contralateral to the EEG focus in four. Brain computed tomography and/or magnetic resonance imaging revealed abnormal findings in 10 of the 13 patients, as shown in Table 1. Coincidence of the EEG focus and the lesion observed on neuroimaging was seen in only three cases. Other cases showed no correlation. EEG revealed unilateral periodic lateralized epileptiform discharges in 11 cases and bilateral periodic lateralized epileptiform discharges in 2. After improvement of the consciousness disturbance, EEG showed no periodic lateralized epileptiform discharges in any patients. As to prognosis, two died, three had epilepsy and mental retardation, one had epilepsy and right hemiplegia, two had mental retardation, and five had no neurologic sequelae.

Discussion

Limited information is available regarding the clinical correlates of periodic lateralized epileptiform discharges, especially in children. Snodgrass et al reviewed 586 cases of periodic lateralized epileptiform discharges reported in the literature and found the etiologies to be cerebrovascular accidents (35%), mass lesions (26%), infections (6%), metabolic abnormalities (9%), anoxia (2%), and others (22%) in adults and children.[4] Garg et al reported no difference between children and adults in clinical characteristics.[5] In the 15 patients in their study, the etiologies of the periodic lateralized epileptiform discharges were liver failure in 2, central nervous system infections in 4, hypoxic-ischemic encephalopathy in 1, burn with dehydration in 1, embolic stroke in 1, leukemia in 3, and lymphoma in 1. Eleven had periodic lateralized epileptiform discharges, and four bilateral periodic lateralized epileptiform discharges. Eight patients died, and seven survived. Hamano et al reported six children presenting periodic lateralized epileptiform discharges aged 3 days to 7 years.[6] The etiologies were encephalitis in two, purulent meningitis in one, acute infantile hemiplegia in one, infarction in one, and intracranial bleeding in one. Raroque et al reported 18 pediatric patients with periodic lateralized epileptiform discharges aged from 3 months to 14 years.[7] The etiologies were meningoencephalitis in seven, anoxia in four, tumors in three, stroke in one, thallium toxicity in one, epilepsy in one, and static encephalopathy in one. Previously, the presence of periodic lateralized epileptiform discharges has been taken to be indicative of focal viral encephalitis, particularly herpes encephalitis. However, in previous series, as well as in our own, no cases of herpes encephalitis were positively identified. Thus, in children, the association of periodic lateralized epileptiform discharges with herpes encephalitis is likely to be quite infrequent.

Influenza-associated encephalopathy, nonherpetic limbic encephalitis, and theophylline seizures were the major causes of periodic lateralized epileptiform discharges in our cases. Although an influenza-associated encephalopathy epidemic is unique in Japanese children, a patient with influenza B–associated encephalopathy characterized by periodic lateralized epileptiform discharges has also been reported.[8] Theophylline-associated seizures are almost always focal and should be considered one of the causes of metabolic insults that can trigger periodic lateralized epileptiform discharges.[9] Nonherpetic limbic encephalitis has also been reported to involve periodic lateralized epileptiform discharges frequently.[2] Bilateral periodic lateralized epileptiform discharges in *Mycoplasma* encephalitis have been reported in two cases.[10] However, their importance as a cause of periodic lateralized epileptiform discharges was not fully mentioned previously. We should pay attention to these disorders when we see periodic lateralized epileptiform discharges in children.

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References

1. Chatrian GE, Shaw GM, Leffman H: The significance of periodic lateralized epileptiform discharges in EEG: An electroencephalographic, clinical and pathological study. *Electroencephalogr Clin Neurophysiol* 1964;17:177–193.
2. Yoshikawa H, Abe T: A child with non-herpetic acute limbic encephalitis. *No To Hattatsu* 2003;35:429–431.
3. Kurihara T, Shoji H, Kaji M, et al: Non-herpetic acute limbic encephalitis. *Clin Neurol* 1994;34:1083–1088.
4. Snodgrass SM, Tsuburaya K, Ajimone-Marsan C: Clinical significance of periodic lateralized epileptiform discharges: Relationship with status epilepticus. *J Clin Neurophysiol* 1989;6:159–172.
5. Garg BP, Patel H, Markand ON: Clinical correlation of periodic lateralized epileptiform discharges in children. *Pediatr Neurol* 1995;12:225–229.
6. Hamano K, Iwasaki N, Takeya T, et al: Clinical significance of periodic lateralized epileptiform discharges in children with relation to level of consciousness. *Pediatr Neurol* 1994;11:28–32.
7. Raroque HG Jr, Wagner W, Gonzales PC, et al: Reassessment of the clinical significance of periodic lateralized epileptiform discharges in pediatric patients. *Epilepsia* 1993;34:275–278.
8. Kurita A, Furushima H, Yamada H, et al: Periodic lateralized epileptiform discharges in influenza B-associated encephalopathy. *Intern Med* 2001;40:813–816.
9. Bahls FH, Ma KK, Bird TD: Theophylline-associated seizures with "therapeutic" or low toxic serum concentrations: Risk factors for serious outcome in adults. *Neurology* 1991;41:1309–1312.
10. Hulihan JF, Bebin EM, Westmoreland BF: Bilateral periodic lateralized epileptiform discharges in *Mycoplasma* encephalitis. *Pediatr Neurol* 1992;8:292–294.

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Case report

Carbamazepine-induced abnormal pitch perception

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Abstract

A 7-year-old boy began to complain that his pitch perception was decreased just after oral medication with carbamazepine was initiated for the treatment of epilepsy. When he played the piano, he felt as if he had played a musical note of almost a half pitch lower than he had. His pitch perception recovered soon after the cessation of carbamazepine. A 14-year-old girl noted a lowered pitch of music sounds while she played the piano just after the administration of carbamazepine for the treatment of epilepsy. Carbamazepine was withdrawn and the auditory symptoms disappeared. Both patients were musically trained. Reversible pitch perception abnormalities are a rare adverse effect of carbamazepine, however, the clinical features of the reported cases were similar; they were musically trained, young, female and Japanese. Although the mechanism remains unclear, we have to pay attention to this subtle adverse effect when we treat epileptic patients with carbamazepine.

Keywords: Carbamazepine; Auditory disturbance; Pitch perception

1. Introduction

Carbamazepine is a first-line agent for localization-related epilepsy, and one of the most popular anticonvulsants used in children. However, carbamazepine has some adverse effects like other antiepileptic drugs. Among the adverse effects of carbamazepine, drowsiness, vertigo, headache and ataxia have been reported as adverse neurotoxic effects [1]. Auditory disturbance associated with carbamazepine medication, such as hyperacousis and tinnitus, has been rarely reported [2], and transient disturbance of auditory pitch perception has also been rarely reported, mainly in young Japanese people [2–11]. However, the mechanism causing such auditory disturbance remains unknown. We report here two Japanese children, a 7-year-old boy and a 14-year-old girl, complaining of peculiar symptoms, such as disturbance of auditory pitch perception only during the administration of carbamazepine. We also review reported cases showing similar symptoms.

2. Case report

2.1. Case 1

This 7-year-old normally developed boy was born without any complications. The family and prenatal histories were not contributory. He experienced a febrile convulsion at the age of 1 year. He had learned the piano since the age of 6 years, and he was considered to have good sound perception. At the age of 7 years, he developed a generalized tonic-clonic convulsion lasting for about 2 min, and therefore he was brought to our hospital. The routine laboratory findings were unremarkable. Cranial computed tomography revealed no abnormal findings. Electroencephalography revealed infrequent isolated spikes in the right frontal area. He was suspected of having idiopathic localization-related epilepsy and so oral administration of carbamazepine of the dosage of 100 mg (body weight 22 kg) was initiated. Just after that, he noticed apparent lowering of the pitch of a telephone ringing, game sounds, and various other everyday mechanical noises. He never noticed tinnitus or reduced hearing ability as to ordinal sounds. When he played a piano, every piano note sound a half tone lower than usual. He never complained of anything other than this abnormality of auditory pitch perception. At that time his blood concentration of carbamazepine was 6.24 μg/ml, which was within normal limits (4–12 μg/ml). One month after the beginning of carbamazepine

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Table 1
Profiles of carbamazepine-induced pitch perception abnormality under 10 years of age[a]

Case	Age/sex	Music education	Diagnosis	CBZ dose/day (mg)	CBZ BC (μg/ml)	Duration before symptoms (days)	Symptoms	Prognosis
1	4/F	+	Epilepsy	100		1	Half tone lower	Recovery
2	9/M	−	BECCT	400	8.2	3	Lower pitch	Recovery
3 (case 1)	7/M	+	FLE	100	6.4	1	Half tone lower	Recovery

[a] CBZ, carbamazepine; BC, blood concentration; BECCT, benign epilepsy of childhood with centro-temporal foci; and FLE, frontal lobe epilepsy.

administration, we replaced the carbamazepine with zonisamide. Thereafter he never complained of the auditory pitch perception disturbance, again.

2.2. Case 2

This 14-year-old girl with normal growth had trained on the piano for several years, wishing to major in music at college. Her family history was not contributory. She had no seizures until the age of 14 years, when she developed nausea, unconsciousness and urine incontinence during an examination at her junior high school. She was transferred to our hospital, where cranial computed tomography revealed no abnormal findings. Routine laboratory examination disclosed no abnormal findings. Electroencephalography revealed infrequent isolated spikes in the bilateral frontal area. So she was diagnosed as having frontal lobe epilepsy, and so the oral administration of carbamazepine at the dosage of 250 mg (body weight 48 kg) was started. Thereafter, she developed no seizures. After carbamazepine therapy had been initiated, she complained that sounds such as those of music instruments, the chime at her school, and telephone ringing seemed to have a lower pitch. She felt something strange only when she played a piano. However, she never complained of reduced hearing ability. One week after the initiation of carbamazepine, she visited our hospital complaining that perceived sounds were of a lower tone than previously. Although her blood concentration of carbamazepine was not measured, we considered her pitch perception disturbance was caused by the carbamazepine. So the carbamazepine was replaced with clonazepam. The next morning after the cessation of carbamazepine, her auditory disturbance had disappeared completely. Thereafter, she has never complained of abnormal pitch perception.

3. Discussion

Our two patients showed similar symptoms such as the reversible disturbance of pitch perception without any reduction in hearing ability. These symptoms developed just after the initiation of carbamazepine administration, and disappeared after the cessation of carbamazepine. Also, case 1 showed half tone lowering, which is compatible with a typical carbamazepine-induced pitch perceptional deficit. So, in our two cases, carbamazepine is considered to have been the most probable cause of the transient pitch perception abnormality [3,4,7,8].

To the best of our knowledge, thirteen patients showing similar symptoms have been reported previously [2–11]. The 15 patients including our two were aged 4–42 years, with a mean age of 19.0 ± 11.2 years. The patients were usually young, elder ones not being reported. Seven of the 15 cases were under 15 years. However, patients under 10 years were rare, only three such patients having been reported, which are summarized in Table 1. Our case 1 was 7 years old, i.e. he is the second youngest patient among the reported cases [3,4]. Also, children under 3 years of age have not been reported, because they are too young to be aware of any symptoms if they have pitch perceptional abnormalities or their pitch perception ability might still be immature. In all reported cases, the symptoms were reversible without any neurological sequalae. Eight showed semitone lowering [3,4,7,8,9,11], one tone lowering [6], three pitch lowering [3,5], and three disturbance of pitch perception [2,10]. The blood concentrations of carbamazepine ranged from 4.3 to 13.6 μg/ml. Symptoms developed from a few hours to 2 weeks after the initiation of carbamazepine administration. Fourteen of the 15 patients were Japanese. It is unclear whether or not some genetic disposition exists. Twelve of the 15 reported patients were female. MacPhee et al. [12] reported that the total choice reaction time in psychomotor performance was significantly more impaired in females. Females were more frequently affected than males. However, two of the three male patients were under 10 years of age. In younger children, female predominance might not be present. Thirteen patients had studied a musical instrument, such as the piano or cello. Chaloupka et al. [11] demonstrated that their patient, who was an absolute pitch possessor, noticed a downward shift of the perceived pitch by one semitone upon the administration of carbamazepine, and some of the other reported cases were also suspected to be absolute pitch possessors. However, it remains unknown whether such abnormal pitch perception due to carbamazepine is a common occurrence, or whether it can be only recognized by persons who are well trained in music.

The mechanism by which carbamazepine disturbs pitch perception is unknown. Also, it remains unknown whether or not carbamazepine acts on the peripheral or central nerve system. The serum levels of carbamazepine in the reported cases were within normal limits, so a neurotoxic effect due

to an overdose was not probable. Although, prolongation of the I–III and I–V latencies of the auditory brain stem response has been reported in carbamazepine-treated patients [13], the auditory brain stem response of the reported patients with abnormal pitch perception was normal. Chaloupka et al. [11] suspected that the cause of this adverse effect may be due to subtle changes in the mechanical properties of the organ of Corti possibly induced by carbamazepine. Another possibility is that carbamazepine, a sodium cannel blocker, might be acting at the level of muscle sarcolemma and thus affecting the tiny but sensitive stapedius muscle that determines the tension on the tympanic membrane that mechanically perceives sound waves, hence pitch. Other mechanisms such as sensory amusia, tone-deafness, and a sound recognition deficit have also been suspected. However, there was no evidence as to which is the case. The exact incidence of this subtle adverse effect is unknown, however, it is suspected that this carbamazepine-induced pitch perception abnormality may be more frequent than we thought, so we have to pay attention to this subtle adverse effect when treating epileptic children with carbamazepine.

References

[1] Gayford JJ, Redpath TH. The side-effects of carbamazepine. Proc R Soc Med 1969;62:615–616.
[2] Tateno A, Morisawa K, Sawai K, Koya N. Three cases of partial epilepsy accompanied by hearing disorder during CBZ medication (in Japanese). Shonika Rinsho 1993;46:323–326.
[3] Tateno A, Omura I. Two cases of auditory disturbance caused by carbamazepine (in Japanese). No To Hattatsu (Tokyo) 2000;32:420–423.
[4] Nihei K, Naito Y. Two cases of absolute pitch perception caused by carbamazepine. J Jpn Epil Soc 1997;15:S68–S69.
[5] Kashihara K, Imai K, Shiro Y, Shohmori T. Reversible pitch perception deficit due to carbamazepine. Int Med 1998;37:774–775.
[6] Tsuji S, Horiguchi A, Yamashita H, Kagaya Y, Yokota N, Yamashiro N. Whole tone down induced by carbamazepine in a patient with bipolar II disorder (in Japanese). Seishin Igaku 1998;40:1213–1215.
[7] Mabuchi K, Hayashi S, Nitta E, Takamori M. Auditory disturbance induced by carbamazepine administration in a patient with secondary generalized seizure. Clin Neurol 1995;35:553–555.
[8] Senjo M. A case of psychogenic reaction whose tone was flatted by carbamazepine (in Japanese). Seishin Igaku 1995;37:649–651.
[9] Emori K, Uehara T, Murata M, Kurachi M. A case of complex partial seizure showing reversible semitone lowing during the elevation of CBZ blood concentration. J Jpn Epil Soc 2000;18:S71.
[10] Onodera M, Hagino T. A case report on auditory disturbance secondary to carbamazepine (in Japanese). Nippon Jibiinkoka Gakkai Kaiho 1994;97:S562.
[11] Chaloupka V, Mitchell S, Muirhead R. Observation of a reversible, medication-induced change in pitch perception. J Acoust Soc Am 1994;96:145–149.
[12] MacPhee GJA, Goldie C, Roulston D, Potter L, Agnew E, Laidlaw J, et al. Effect of carbamazepine on psychomotor performance in native subjects. Eur J Clin Pharmacol 1986;30:37–42.
[13] Medaglini S, Filippi M, Smirne S, Ferini-Strambi L, Giusti MC, Poggi A, et al. Effects of long-lasting antiepileptic therapy on brainstem auditory evoked potentials. Neuropsychobiology 1988;19:104–107.

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CASE REPORT

Persistent hyperinsulinemic hypoglycaemia followed as benign infantile convulsion

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An 18-month-old boy developed seizures at 3 months of age. He developed normally and, his EEG and brain CT revealed no abnormal findings. The blood sugar level was normal at that time, thus he was diagnosed as having benign infantile convulsion. At 7 months of age seizures reappeared, and hypoglycaemia associated with hyperinsulinism was observed during the seizures. With conservative therapy his blood sugar level was well controlled and he had no further seizures. Hypoglycaemic seizures are sometimes misdiagnosed as epilepsy. We have to pay attention to hyperinsulinemic hypoglycaemia when we see seizures with normal EEG even in infants.

Key words: hyperinsulinism; hypoglycaemia; benign infantile convulsion; epilepsy.

INTRODUCTION

Hyperinsulinemic hypoglycaemia causes hypoglycaemic seizures during the neonatal and infant periods, and sometimes these seizures are misdiagnosed as epilepsy[1–3]. When patients show normal development except seizures, normal electroencephalography (EEG), they could also meet the criteria of 'benign infantile convulsion'[4]. Persistent hypoglycaemia leads to neuronal injury, therefore, efficient diagnosis and treatment are essential. So, even in cases of infantile convulsions with normal EEG and normal development, hyperinsulinism should be ruled out as early as possible.

CASE REPORT

This 18-month-old Japanese boy was born without any complications at 37 weeks of gestation. The blood sugar level was normal at birth. One week after birth, his parents noticed that he sometimes showed cyanosis during sucking of milk. At 3 months of age, generalised tonic convulsions lasting for about 1–2 minutes occurred, twice or three times per week. So, he was admitted to our hospital at 4 months of age. On admission, physical examination disclosed no abnormal findings. Routine laboratory examinations revealed no abnormal findings including blood sugar. Brain CT and EEG revealed no abnormal findings. The oral administration of carbamazepine was started and the seizures ceased completely. So, he was tentatively diagnosed as having benign infantile convulsion because of normal development no neurological findings, no EEG abnormalities, and a favourable response to carbamazepine. However, at 6 months of age, generalised tonic convulsions occurred several times, and the dosage of carbamazepine was increased, but it failed to stop the seizures. During the seizures, the blood sugar level was measured and found to be low. His fasting blood sugar level and immunoreactive insulin level (IRI) were 38 mg/dl and 21.3 μU/ml, respectively. Also the IRI/blood sugar (BS) ratio was 0.56. Abdominal ultrasonography and CT disclosed no pancre-

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atic tumour. Based on these data, at 7 months of age, he was diagnosed as having hyperinsulinemic hypoglycaemia.

The intravenous infusion of glucose increased the blood sugar level, and the seizures ceased. The oral administration of diazoxide was begun. Then baby food with high carbohydrate and low protein contents was started. Thereafter, he showed neither hypoglycaemia nor convulsions. After the oral administration of diazoxide, the fasting blood sugar level, IRI and IRI/BS ratio became 65 mg/dl, 5.0 μU/ml and 0.077, respectively. At present, he developed normally and had no seizures.

DISCUSSION

The prognoses of epilepsies in the first year of life are usually poor, however, several authors[4, 5] have reported that benign infantile convulsion or epilepsy is present. Benign infantile convulsion[4] is defined as generalised tonic convulsions occurring with no apparent cause in neurodevelopmentally normal infants aged under 2 years with normal interictal EEG. Watanabe *et al.*[5] proposed a similar condition, benign partial epilepsy in infancy (BPEI), which is defined as follows: complex partial seizures and/or secondarily generalised seizures, normal psychomotor developmental and neurological findings before onset, normal interictal EEG, normal cranial CT and magnetic resonance imaging and no seizures during the first 4 weeks of life. The clinical features of our patient also met the criteria of benign infantile convulsion[4] or BPEI[5], if hypoglycaemia was not present. Some patients with BPEI were misdiagnosed at the first presentation.

The onset of persistent hyperinsulinemic hypoglycaemia can occur from the neonatal to the infantile period, and is characterised by hypoglycaemia associated with hyperinsulinemia. It is diagnosed using the criterion of an IRI/BS ratio of over 0.3. When other disorders causing hypoglycaemia can be ruled out, the diagnosis of persistent hyperinsulinemic hypoglycaemia can be made. In persistent hyperinsulinemic hypoglycaemia, the initial symptoms of the hypoglycaemia are jitters, bad temper, hypotonia, cyanosis, unconsciousness and convulsions. Hypoglycaemic seizures are not rare in hypoglycaemic patients. Izumi *et al.*[2] reported five cases of hyperinsulinemic hypoglycaemia showing various types of hypoglycaemic seizures, i.e. apnea, erratic seizures, generalised tonic seizures and myoclonic seizures. However, the frequency of hypoglycaemic seizures was not fully investigated, and sometimes the hypoglycaemic seizures were misdiagnosed as epilepsy[1–3]. Neonatal and infantile hypoglycaemia in the brain may cause permanent neurological sequelae, such as epilepsy and mental retardation[3]. So, early diagnosis and treatment is important to prevent permanent neurological sequelae. Concerning the differential diagnosis of benign infantile convulsion, hypoglycaemic seizures in persistent hyperinsulinemic hypoglycaemia should be added and the blood sugar level should be examined frequently even if the interictal blood sugar is normal.

REFERENCES

1. Stanley, C. A. Hyperinsulinism in infants and children. *Pediatric Clinics of North America* 1997; **44**: 363–374.
2. Izumi, T., Takeshige, H., Arai, T. *et al.* Prospective study of nesidioblastosis in newborns and infants: hypoglycemic seizures epileptogenesis and the significance of the C-peptide suppression test in pancreatectomy. *Acta Paediatrica Japonica* 1997; **39**: 10–17.
3. Menni, F., de Lonlay, P., Sevin, C. *et al.* Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001; **107**: 476–479.
4. Fukuyama, Y. Borderland of epilepsy with special reference to febrile convulsions and so called infantile convulsions. *Seishin-igaku (Clinical Psychiatry)* 1963; **5**: 211–223.
5. Watanabe, K., Negoro, T. and Aso, K. Benign partial epilepsy with secondarily generalized seizures in infancy. *Epilepsia* 1993; **34**: 635–638.