軽度の分析

図 55.異常行動（軽度）の発熱週と発生動向調査
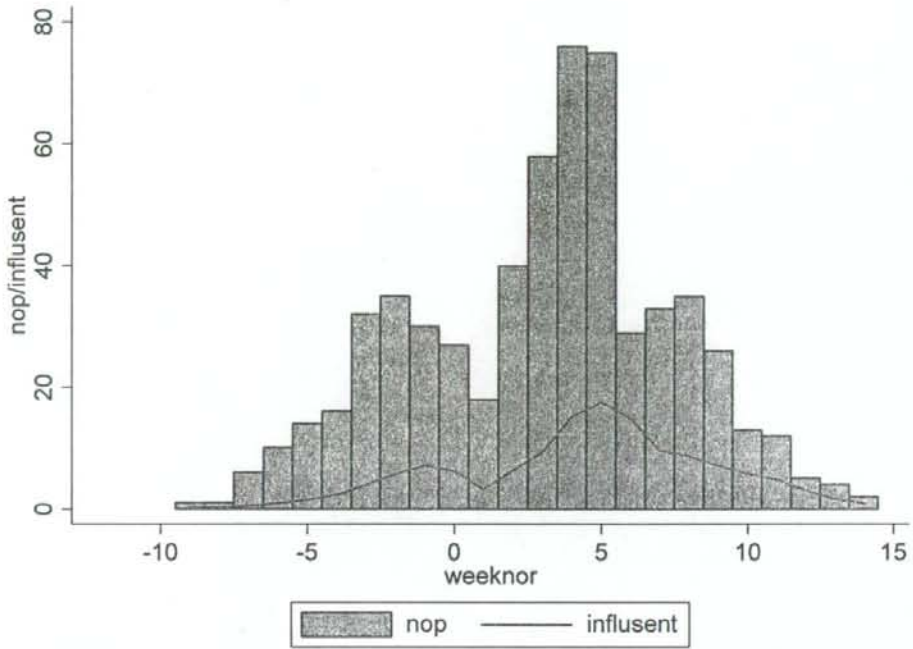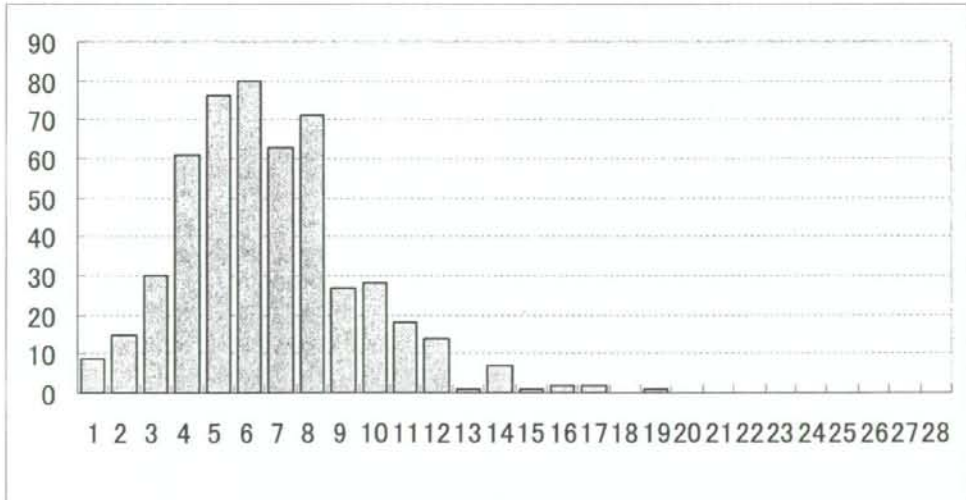

図 56.患者の年齢 n=520

平均値 6.6 中央値 6

図 57.患者の性別 n=520
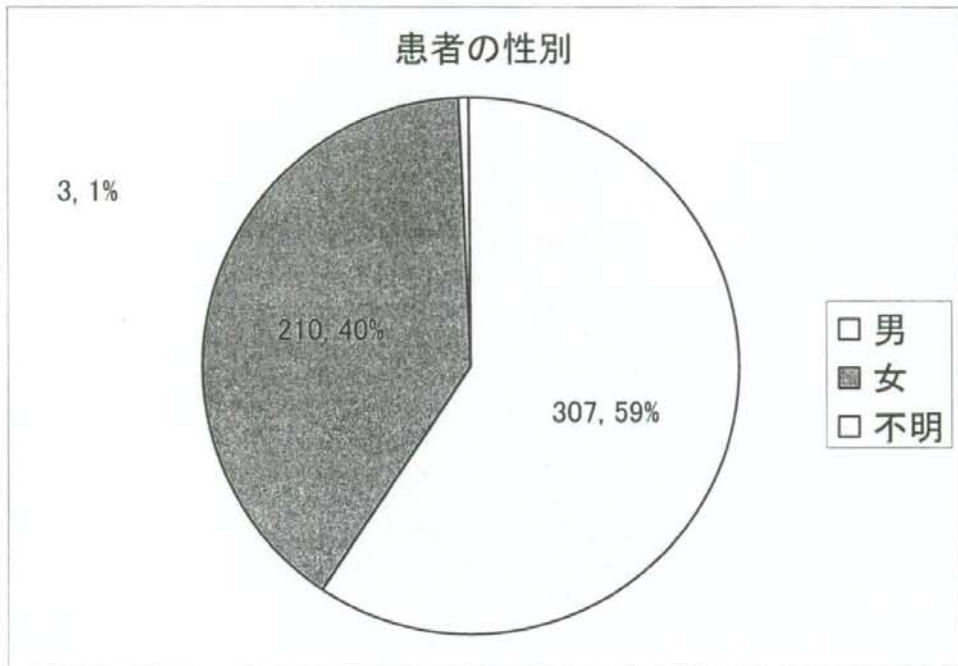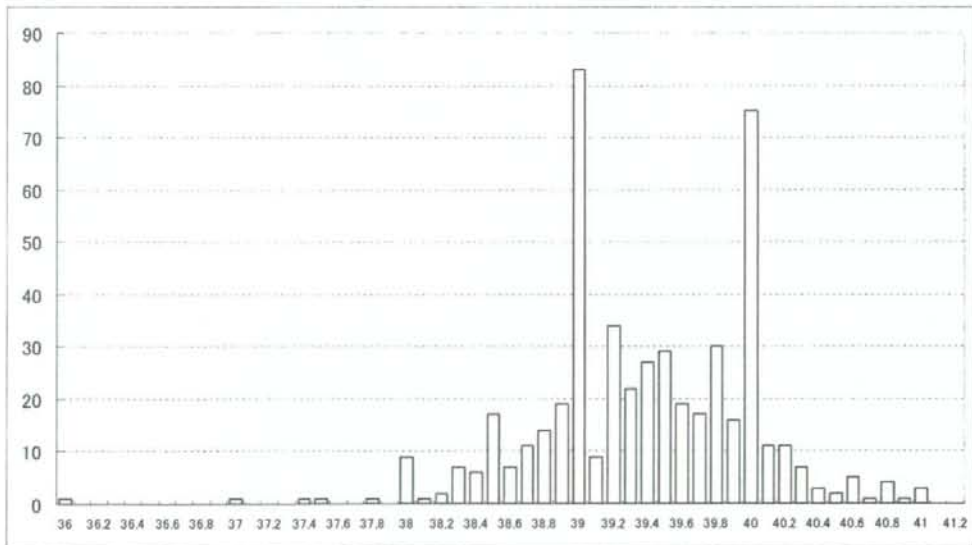
患者の性別

3, 1%

210, 40%

307, 59%

□ 男
■ 女
□ 不明

図 58.最高体温 n=520

平均値 39.39 中央値 39.4

図 59.インフルエンザ迅速診断キットの実施の有無 n=520

インフルエンザ迅速診断キットの実施の有無

6,
1%

514,
99%

有
無
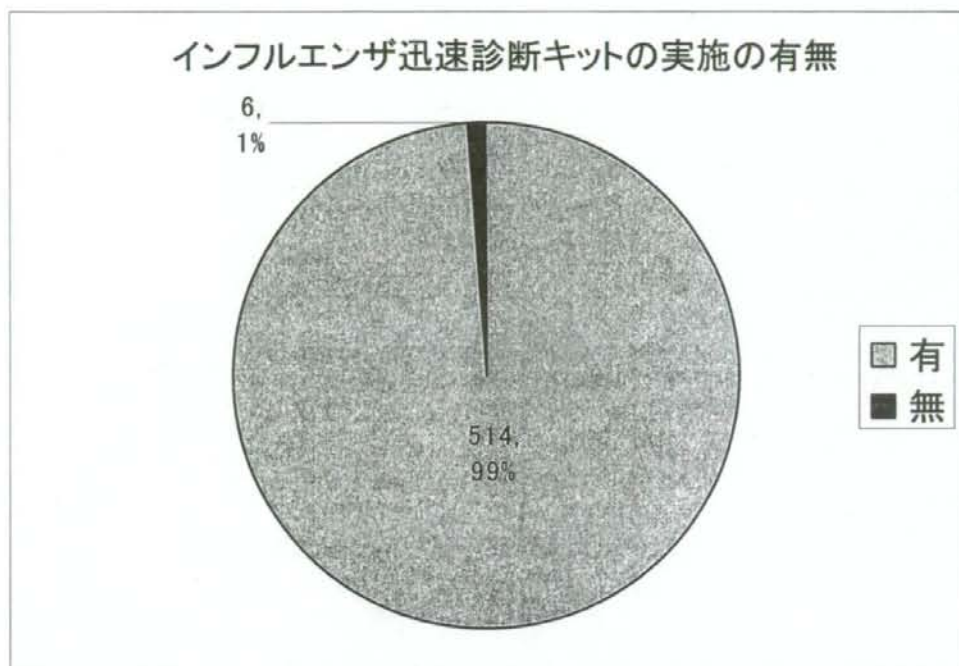
図 60.迅速診断キットによる検査結果 n=519

迅速診断キットによる検査結果

3,
1%

9,
3%

16,
3%

489,
93%

陽性(A型)
陽性(B型)
陰性
不明

図 61.罹患前半年間の予防接種歴 n=520

罹患前半年間の予防接種歴

61, 12%

125, 24%

279, 53%

55, 11%

- □ 1回
- ▓ 2回
- □ 不明
- □ 無し
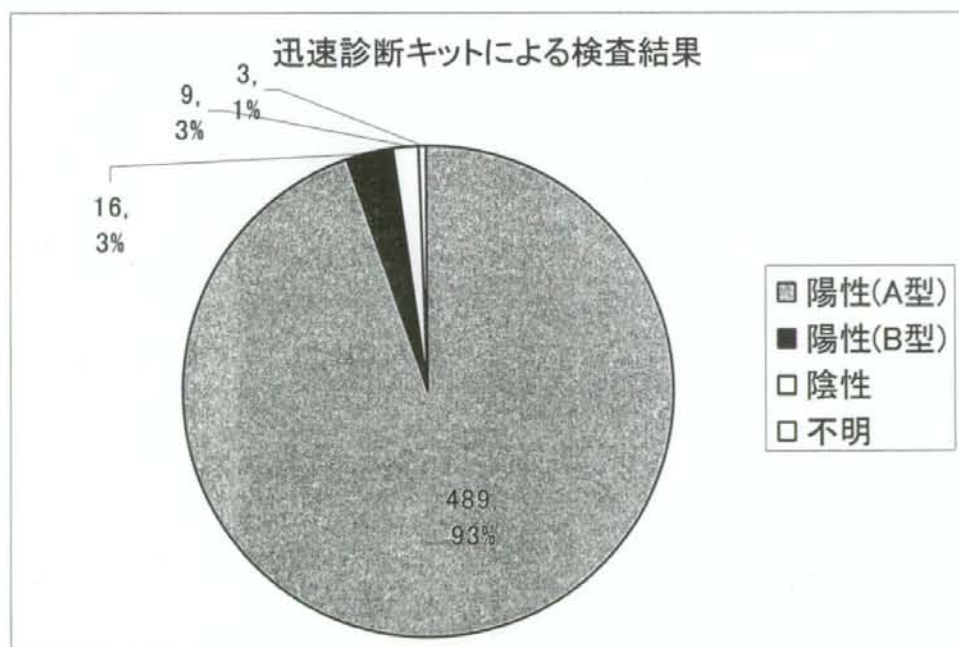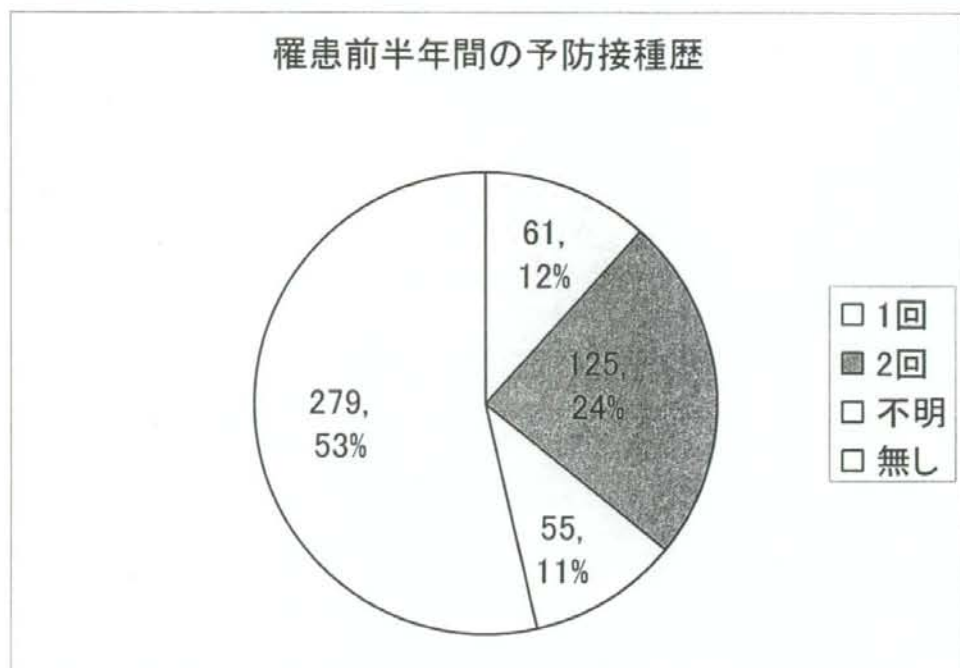
図 62.タミフル(リン酸オセルタミビル)服用の有無 n=520

タミフル(リン酸オセルタミビル)服用の有無

35, 7%

211, 41%

274, 52%

- □ 有
- ▓ 無
- □ 不明

図 63.タミフル（リン酸オセルタミビル）服用の有無の性別

男性n＝307

不明
7%

タミフル服用
の有り
37%

タミフル服用
の無し
56%

女性n＝210
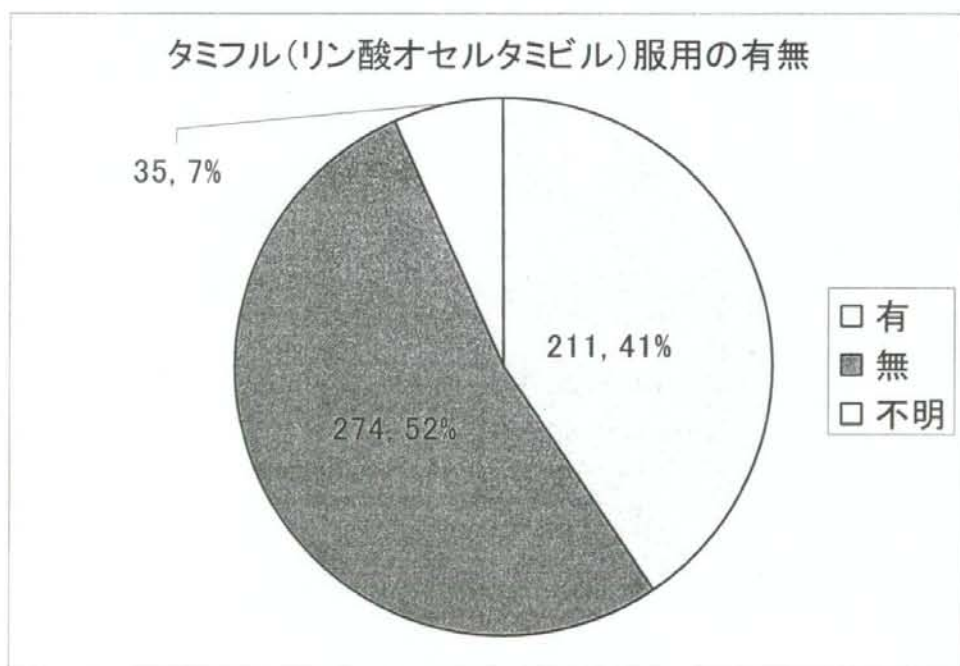
タミフル服
用の無し
52%
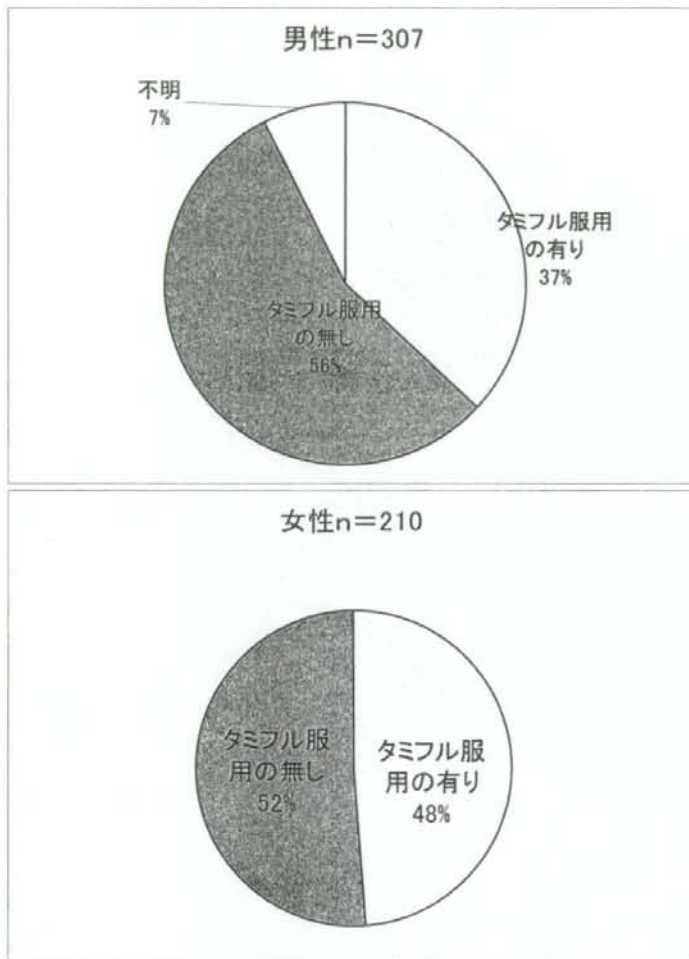
タミフル服
用の有り
48%

図 64.タミフル（リン酸オセルタミビル）服用の有無の年齢別

タミフル服用有りn＝206
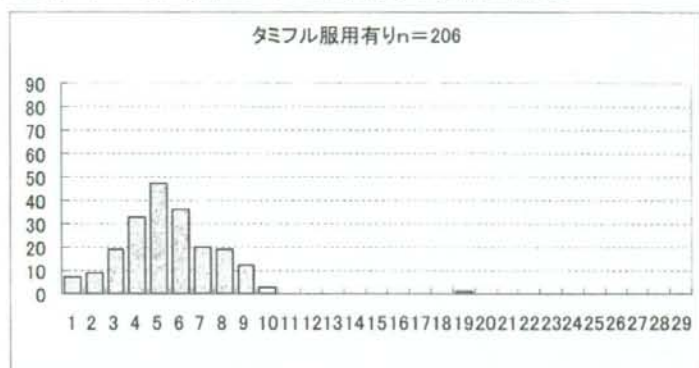
平均値 5.40　中央値 5

タミフル服用無しn＝265
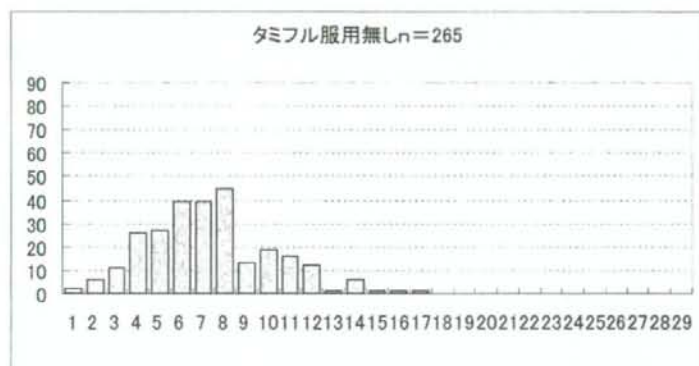
平均値 7.26　中央値 7

図 65.シンメトレル（塩酸アマンタジン）服用の有無 n=520

シンメトレル（塩酸アマンタジン）服用の有無

4, 1%

112, 22%

404, 77%

□ 有
■ 無
□ 不明
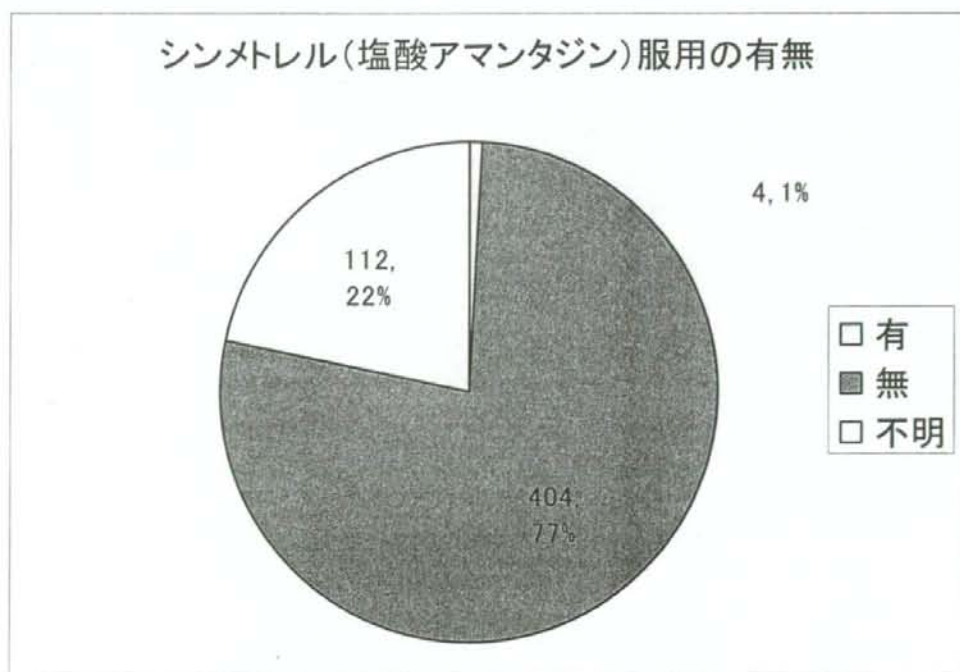
図 66.リレンザ(ザナミビル)使用の有無 n=520

リレンザ(ザナミビル)使用の有無

97,
19%

72,
14%

351,
67%

□ 有
▨ 無
□ 不明
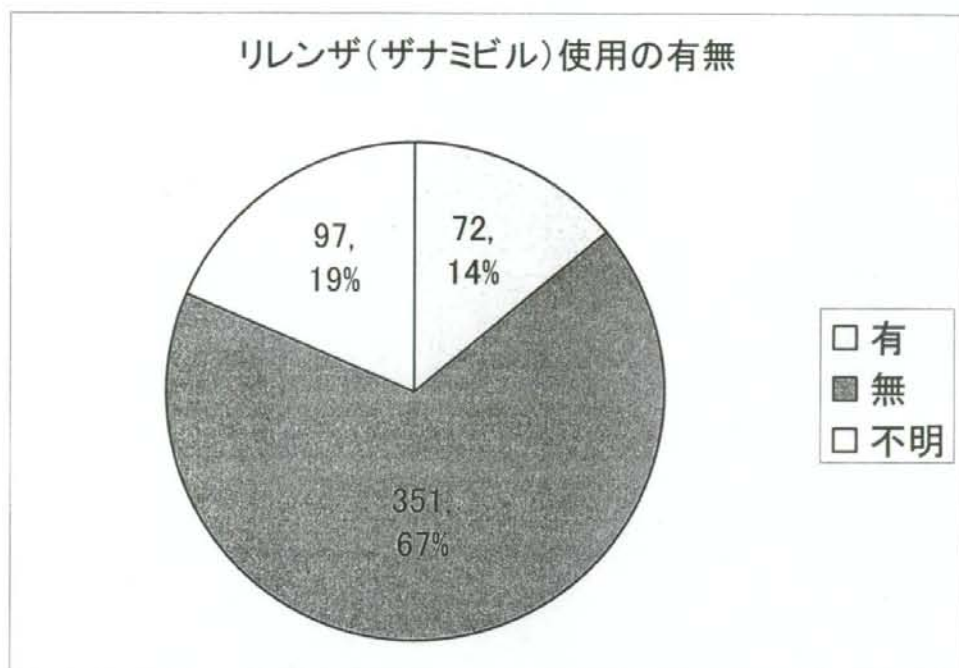
図 67.アセトアミノフェン服用の有無 n=520

アセトアミノフェン服用の有無

120,
23%

144,
28%

256,
49%

□ 有
▨ 無
□ 不明

図 68.異常行動と睡眠の関係 n=520

異常行動と睡眠の関係

- □ 異常行動は覚醒していて徐々に起こった
- ▨ 異常行動は眠りから覚めて直に起こった
- □ 不明
- □ その他

3, 1%
125, 24%
122, 24%
270, 52%

図 69.異常行動の分類（複数回答）

異常行動の分類

分類	件数
突然走り出す	26
飛び降り	0
会話中、突然話が通じなくなる	52
おびえ・恐慌状態	127
無いものが見えると言う	122
激しいうわごと・寝言	174
わめく・泣きやまない	96
暴力・興奮状態	33
はねる	14
徘徊	52
無意味な動作の繰り返し	69
その他	239
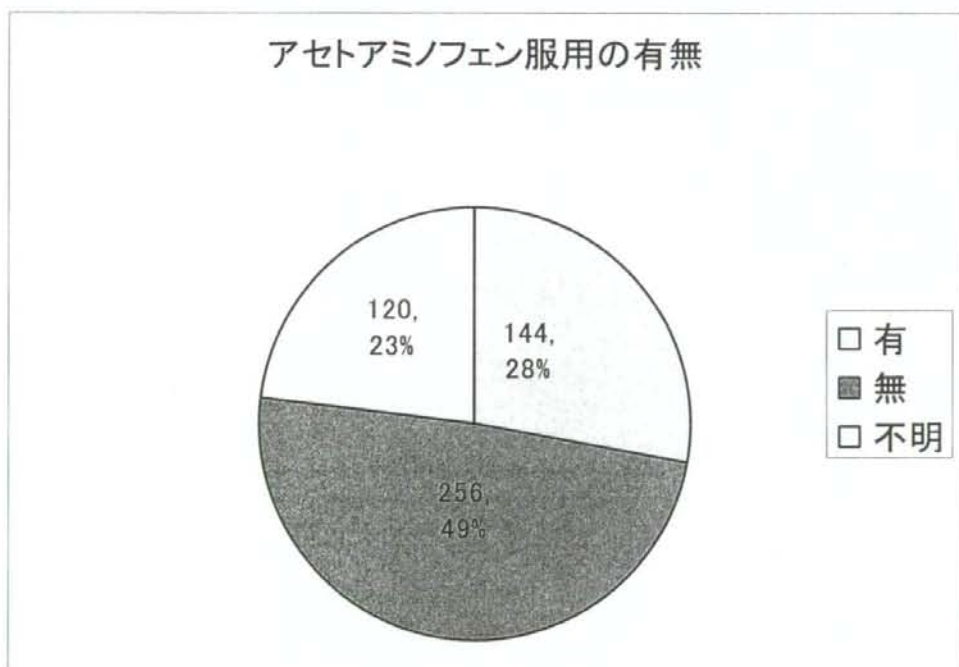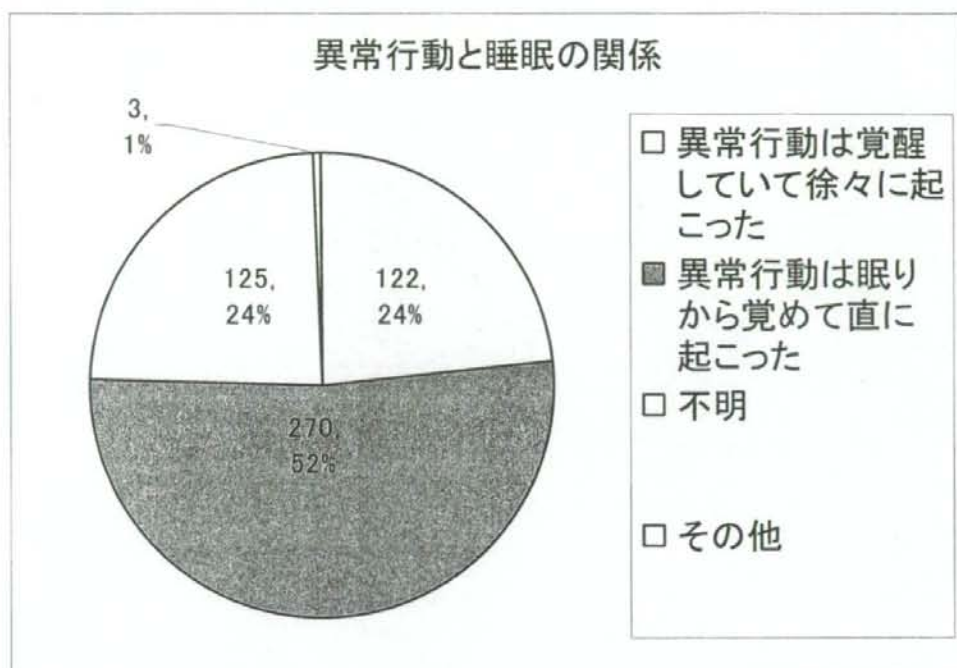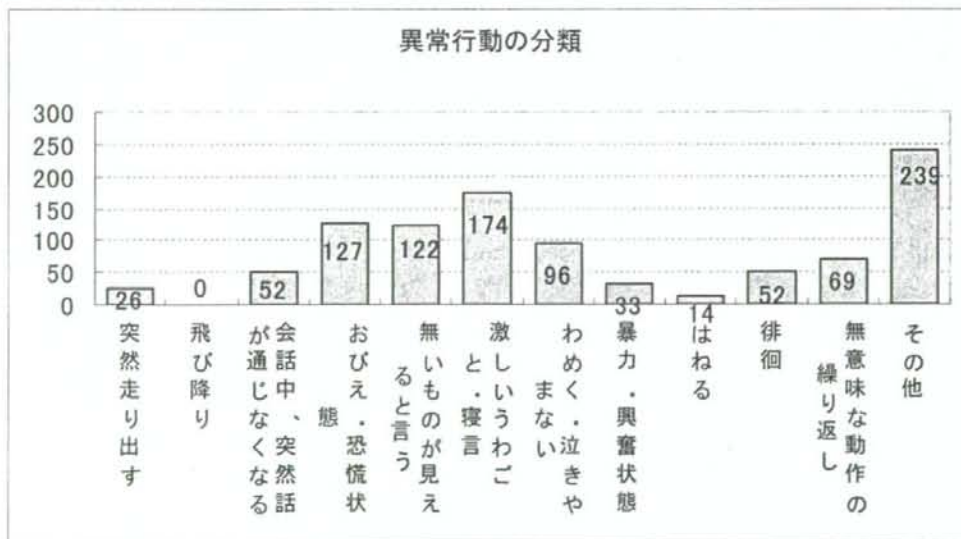
図 70.タミフル有無と異常行動と睡眠の関係

タミフル服用有り群

異常行動は覚醒していて徐々に起こった, 41, 19%

異常行動は眠りから覚めて直に起こった, 106, 51%

その他, 2, 1%

不明, 62, 29%

タミフル服用無し群

その他, 1, 0%

不明, 52, 19%

異常行動は覚醒していて徐々に起こった, 73, 27%

異常行動は眠りから覚めて直に起こった, 148, 54%
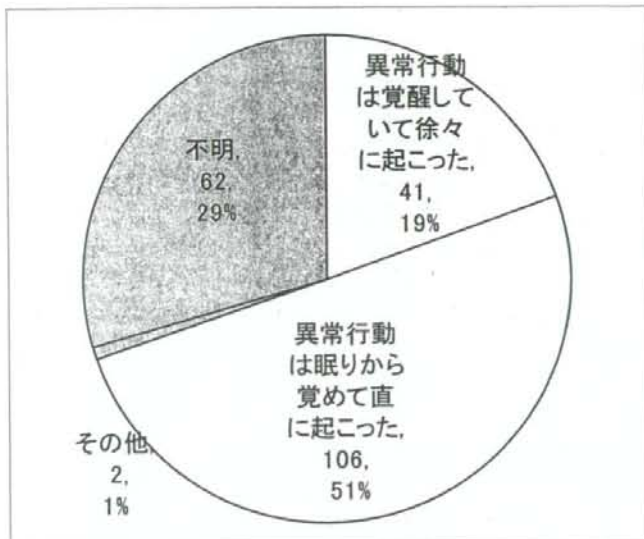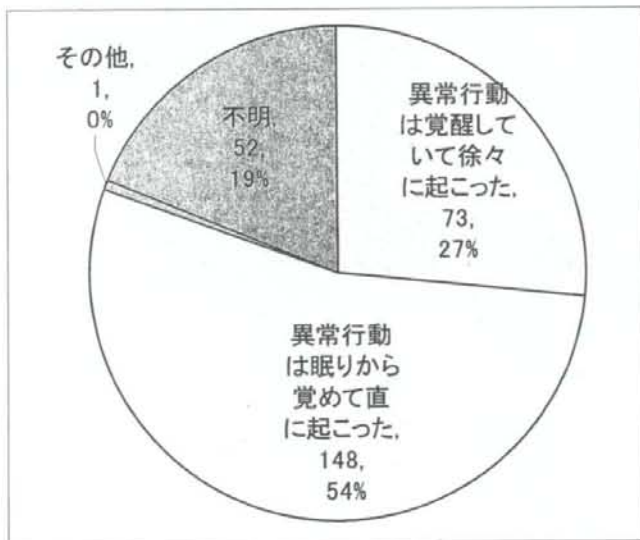
Ⅲ　研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
宮崎千明（共著）	パルボウイルスB19感染症	大関武彦、近藤直美総編集	小児科学第3版	医学書院	東京	2008	737-738
宮崎千明（共著）	日本脳炎ワクチンの接種法	五十嵐隆、渡辺博編集	小児科臨床ピクシス4予防接種	中山書店	東京	2008	146-147
宮崎千明（共著）	日本脳炎ワクチンの接種法	五十嵐隆、渡辺博編集	小児科臨床ピクシス4予防接種	中山書店	東京	2008	148-149
宮崎千明（共著）	日本脳炎の流行状況	五十嵐隆、渡辺博編集	小児科臨床ピクシス4予防接種	中山書店	東京	2008	150-151
宮崎千明（共著）	新旧日本脳炎ワクチンの違い	五十嵐隆、渡辺博編集	小児科臨床ピクシス4予防接種	中山書店	東京	2008	152-153
宮崎千明（共著）	日本脳炎ワクチン未接種者への対応	五十嵐隆、渡辺博編集	小児科臨床ピクシス4予防接種	中山書店	東京	2008	154-155

論文

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nagao Y, Morishima T, Kimura H, Yokota S, Yamashita N, Ichiyama T, Kurihara M, Miyazaki C, Okabe N	Prognostic factors in influrenza-associated encephalopathy	Pediatr Inf Dis J	Vol.27(5)	384-389	2008
藤岡雅司、永井崇雄、落合仁、崎山弘、田原卓浩、寺田喜平、宮崎千明、横田俊一郎、吉川哲史	麻しん及び風しん定期予防接種の接種体制に関する全国自治体への調査報告	日本小児科学会雑誌	Vol.112(10)	1618-1622	2008
宮崎千明	日本脳炎ワクチン	チャイルドヘルス	Vol.11	21－23	2008
宮崎千明	米国における生ワクチン接種の現状	インフルエンザ	Vol.9 No.3	55-59	2008
宮崎千明	新しいワクチンの今後の展望	丹々会会報	Vol.33	27-31	2008

宮崎千明	Hibワクチン	日本臨床	Vol.66(10)	1985-1989	2008
宮崎千明	現在の予防接種の問題点および今後の展望	臨床と研究	Vol.85(9)	1336-1340	2008
宮崎千明	ワクチンの有効性そしてワクチン導入が遅れる訳	日本小児科医会報	Vol36	31-32	2008
Miyazaki C	Japanese encephalitis vaccine	Japan Medical Association J	Vol.51(3)	1-6	2008
宮崎千明	医療従事者と風疹	感染対策 ICT ジャーナル	Vol4(1)	33-37	2008
宮崎千明	米国ACIPと小児のインフルエンザワクチン	小児科臨床	Vol.61(10)	2091-2095	2008

IV　研究成果の刊行物・別刷

原著	Nagao Y, Morishima T, Kimura H, Yokota S, Yamashita N, Ichiyama T, Kurihara M, <u>Miyazaki C</u>, Okabe N	Prognostic factors in influrenza-associated encephalopathy	Pediatr Inf Dis J Vol.27(5)	384-389	2008
原著	藤岡雅司、永井崇雄、落合仁、崎山弘、田原卓浩、寺田喜平、<u>宮崎千明</u>、横田俊一郎、吉川哲	麻しん及び風しん定期予防接種の接種体制に関する全国自治体への調査報告	日本小児科学会雑誌 Vol.112(10)	1618-1622	2008
総説	<u>宮崎千明</u>	日本脳炎ワクチン	チャイルドヘルスVol.11	21−23	2008
総説	<u>宮崎千明</u>	米国における生ワクチン接種の現状	インフルエンザ Vol.9 No.3	55-59	2008
総説	<u>宮崎千明</u>	新しいワクチンの今後の展望	丹々会会報 Vol.33	27-31	2008
総説	<u>宮崎千明</u>	Hibワクチン	日本臨床 Vol.66(10)	1985-1989	2008
総説	<u>宮崎千明</u>	現在の予防接種の問題点および今後の展望	臨床と研究 Vol.85(9)	1336-1340	2008
総説	<u>宮崎千明</u>	ワクチンの有効性そしてワクチン導入が遅れる訳	日本小児科医会報 Vol36	31-32	2008
Research and Reviews	<u>Miyazaki C</u>	Japanese encephalitis vaccine	Japan Medical Association J Vol. 51(3)	1-6	2008
総説	<u>宮崎千明</u>	医療従事者と風疹	感染対策ICTジャーナル Vol4(1)	33-37	2009
その他	<u>宮崎千明</u>	米国ACIPと小児のインフルエンザワクチン	小児科臨床 Vol.61(10)	2091-2095	2008
著書(共著)	<u>宮崎千明</u>	パルボウイルスB19感染症	小児科学第3版 大関武彦、近藤直美総編集 医学書院 東京	737-738	2008
著書(共著)	<u>宮崎千明</u>	日本脳炎ワクチンの接種法	小児科臨床ピクシス4 予防接種 五十嵐隆、渡辺博編集 中山書店 東京	146-147	2008
著書(共著)	<u>宮崎千明</u>	日本脳炎ワクチンの接種法	小児科臨床ピクシス4 予防接種 五十嵐隆、渡辺博編集 中山書店 東京	148-149	2008
著書(共著)	<u>宮崎千明</u>	日本脳炎の流行状況	小児科臨床ピクシス4 予防接種 五十嵐隆、渡辺博編集 中山書店 東京	150-151	2008
著書(共著)	<u>宮崎千明</u>	新旧日本脳炎ワクチンの違い	小児科臨床ピクシス4 予防接種 五十嵐隆、渡辺博編集 中山書店 東京	152-153	2008
著書(共著)	<u>宮崎千明</u>	日本脳炎ワクチン未接種者への対応	小児科臨床ピクシス4 予防接種 五十嵐隆、渡辺博編集 中山書店 東京	154-155	2008

ORIGINAL STUDIES

Prognostic Factors in Influenza-Associated Encephalopathy

Takashi Nagao, MD, Tsuneo Morishima, PhD,* Hiroshi Kimura, PhD,† Syumpei Yokota, PhD,‡
Nobuko Yamashita, PhD,* Takashi Ichiyama, PhD,§ Mana Kurihara, PhD,‖ Chiaki Miyazaki, PhD,¶
and Nobuhiko Okabe, MD, PhD#*

Background: Recently, reports of influenza-associated encephalopathy have increased worldwide. Given the high mortality and morbidity rates attributable to this severe neurologic complication of influenza, we conducted a nationwide study in Japan to identify the prognostic factors.

Methods: We retrospectively evaluated 442 cases of influenza-associated encephalopathy that were reported to the Collaborative Study Group on Influenza-Associated Encephalopathy, which was organized by the Japanese Ministry of Health, Labor, and Welfare in collaboration with hospitals, clinics, and local pediatric practices in Japan between 1998 and 2002. The outcome for each patient was classified as either survival or death. Predictors of death were identified using logistic regression analysis.

Results: Four major prognostic factors for death were found to be significant by multivariate analysis ($P < 0.05$) in the 184 patients for whom we had complete data: elevation of aspartate aminotransferase, hyperglycemia, the presence of hematuria or proteinuria, and use of diclofenac sodium.

Conclusions: We identified patients who had factors associated with a poor prognosis, and these findings might be clinically useful for the management of this illness.

Key Words: influenza-associated encephalopathy, hyperglycemia, hematuria, diclofenac, IL-6, TNF-α

(Pediatr Infect Dis J 2008; 27: 000–000)

Influenza-associated encephalopathy is a severe neurologic complication of influenza characterized by an abrupt onset of seizures and coma within a few days of developing a high fever.[1] The number of patients with influenza-associated encephalopathy in Japan has increased in recent years, with more than 100 children younger than 6 years of age dying annually from this severe disease.[1] Recently, reports of influenza-associated encephalopathy have also increased worldwide.[2,3]

Blood abnormalities, such as thrombocytopenia and elevated serum aspartate aminotransferase (AST), and brain computed tomography (CT) abnormalities are associated with poor outcome.[4] Cyclooxygenase inhibitors, particularly aspirin, are known to cause Reye syndrome.[5,6] In Japan, cyclooxygenase inhibitors such as diclofenac sodium and mefenamic acid, but not aspirin, are widely used as antipyretic drugs in children. We found that some nonsalicylate antipyretic drugs, including diclofenac sodium and mefenamic acid, may be associated with the development of influenza-associated encephalopathy or may affect the severity of the disease.[1] However, we were unable to thoroughly assess the relationship between the use of these medicines and prognosis.

The mortality rate of this disease is as high as 30% without treatment.[1] Therefore, for the administration of intensive care, it is important to identify the factors that affect its prognosis. We investigated 442 cases of influenza-associated encephalopathy reported from 1998 to 2002 in the Collaborative Study Group on Influenza-Associated Encephalopathy organized by the Japanese Ministry of Health, Labor, and Welfare, and analyzed the prognostic factors using multivariate logistic regression analysis. We report several factors related to the poor prognosis of influenza-associated encephalopathy. To our knowledge, this is the first nationwide study of the prognostic factors of influenza-associated encephalopathy.

METHODS

Study Design. Questionnaires were developed by the Collaborative Study Group on Influenza-Associated Encephalopathy to assess the number of cases in all hospitals, clinics, and local pediatric practices (total of 3500 sites) between 1998 and 2002. Subsequently, a second questionnaire was sent to each applicable facility. The second questionnaire requested information on age, sex, virus type, history, flu vaccination record, peak body temperature, symptoms, laboratory data, CT findings, medication, diagnosis, methods of influenza virus infection, and disease outcome. The age, peak body temperature, and laboratory data were provided directly by participant clinicians, the other data were gathered during a subsequent questionnaire. [...illegible...]

ratory data were obtained at admission. Recently, it has been reported that prognosis could be improved by therapies such as methylprednisolone pulse and hypothermia therapy. However, it was not possible to obtain information regarding these therapies for this study.

The study protocol was approved by the Institutional Review Board of Nagoya University Hospital.

Case Definition. Influenza infection was defined on the basis of a positive result on viral culture, viral antigen testing, or viral ribonucleic acid polymerase chain reaction, or a 4-fold or greater rise in paired serum antibody titer test (hemagglutination inhibition or complement fixation test). Patients who did not meet all the criteria were excluded from the study. In viral antigen testing, the influenza type could not be determined in several cases because the diagnosis was made using a viral antigen test that could not distinguish between types A and B influenza. Patients were defined as having influenza-associated encephalopathy if they showed clinical symptoms and signs compatible with acute encephalopathy, such as altered consciousness (ie, delirium, confusion, and cognitive impairment) or loss of consciousness (ie, deep coma, coma, semicoma, stupor, and somnolence), and if these symptoms persisted for more than 24 hours. Patients with meningitis, myelitis, and febrile convulsions without prolonged unconsciousness were excluded. Cases of postictal unconsciousness with prompt recovery were classified as febrile convulsion. All of the cases reported as influenza-associated encephalopathy were reviewed thoroughly by members of the study group to confirm whether the diagnosis was appropriate. Doubtful cases were excluded from further analysis. The outcomes of influenza-associated encephalopathy were defined as survival or death. A survival outcome included all patients who were alive regardless of whether they had sequelae. In total, 442 influenza-associated encephalopathy cases in patients younger than 15 years of age were deemed appropriate for the study. Study participants provided informed consent or assented with parental consent.

Statistical Analysis. The data were analyzed using the Dr. SPSS software package version 2 (SPSS Inc, Tokyo, Japan). Twenty variables were analyzed to formulate a predictive model for death caused by influenza-associated encephalopathy. The variables identified as significant at $P < 0.05$ using univariate logistic regression analysis were entered into a multivariate logistic regression model, and the least significant variables were sequentially removed. In the multivariate logistic regression analysis, the model was adjusted by age, sex, virus type, history of allergy, record of flu vaccination, and use of acetaminophen. In the multivariate logistic regression analysis, a value of $P < 0.05$ was considered statistically significant. A P value between 0.05 and 0.20 was considered to show a tendency toward being a factor for poor prognosis because a risk existed of eliminating important prognostic factors in the logistic regression if the P values were restricted to 0.05. Odds ratios with 95% confidence intervals were also estimated.

RESULTS

nally having influenza-associated encephalopathy, according to the primary questionnaire. In response to the second questionnaire, 585 cases from a total of 340 sites were reported and 442 cases in patients younger than 15 years of age deemed appropriate for further study. These included 97 patients who died and 345 patients who survived.

Of the 442 patients, 331 (74.9%) were between 1 and 6 years old. 232 were male, and 210 were female. No significant differences were observed in incidence or mortality between the sexes; 45 males and 52 females died. The death rates were 32.1%, 22.5%, 13.7%, and 16.4% in 1998–1999, 1999–2000, 2000–2001, and 2001–2002, respectively. We found 372 (84.2%) and 42 (9.5%) cases of type A and type B influenza, respectively. In the other 28 (6.3%) cases, the influenza type could not be determined. Fifty-four cases (22.1%) had a history of febrile convulsions.

Table 1 shows the numbers, percentages, odds ratios, and 95% confidence intervals from the univariate logistic regression analyses for the 20 variables divided by survival and death. In the univariate analyses, 14 variables had statistical significance ($P < 0.05$); peak body temperature of 40–41°C and >41°C, diarrhea; AST level of 100–500 IU/L and >500 IU/L, creatinine phosphokinase level of 200–1000 IU/L and >1000 IU/L, platelet count of $< 10 \times 10^4/\mu$L, blood glucose level of <50 and >150 mg/dL, hematuria or proteinuria, CT showing edema, low-density areas, or hemorrhage; and use of diclofenac sodium and mefenamic acid for fever during influenza virus infection. These variables were retained for multivariate analysis.

The following variables related to patient background were also used in the multivariate analyses, although they were not significantly related to prognosis: age, sex, virus types, allergy history, flu vaccination record, and acetaminophen use. A history of febrile convulsion was excluded because of missing data.

We could not analyze all 442 patients in multivariate analysis because many of the factors with statistical significance in univariate analysis were missing data. A total of 13 of the 16 variables used in multivariate analysis had several missing data points. Thus, a total of 184 patients with complete data were included in multivariate analysis (Fig 1). Reducing the number of cases from 442 to 184 did not significantly alter the percentage of survival and death.

Table 2 summarizes the numbers and percentages of the 184 patients with complete data for these 16 variables and shows the adjusted odds ratios and 95% confidence intervals from multivariate logistic regression analysis. Four significant prognostic factors were used: AST >500 IU/L ($P = 0.04$); blood glucose >150 mg/dL ($P = 0.04$); hematuria or proteinuria ($P = 0.01$); and the use of diclofenac sodium ($P = 0.03$). The following variables showed a tendency toward being factors for poor prognosis: peak body temperature of 39–40°C ($P = 0.18$), 40–41°C ($P = 0.14$), and >41°C ($P = 0.08$); platelet 10 × 10⁴ /μL ($P = 0.18$); blood glucose <50 mg/dL ($P = 0.11$); CT showing edema, low-density areas, or hemorrhage ($P = ...$) ...

TABLE 1.   Characteristics on Admission and Univariate Analysis of Prognostic Factors in the 442 Patients Between 1998 and 2002

Variable	No. Patients		Odds Ratio (95% CI)	P
	Survival (n = 345)	Death (n = 97)		
Age group, yr				
1	22	6	1	
1–6	257	71	1.06 (0.41–2.76)	0.91
6–15	66	17	0.94 (0.33–2.68)	0.92
Sex				
Male	187	45	0.73 (0.47–1.15)	0.17
Female	158	52	1	
Virus types				
Type A	294	78	0.56 (0.28–1.10)	0.11
Type B	29	13	1	
Unclassified	22	6		
Past history				
Allergy				
Yes	21	1	0.16 (0.02–1.21)	0.08
No	324	96	1	
Febrile convulsion				
Yes	16	6	0.80 (0.28–2.07)	0.79
No	329	91	1	
Flu vaccination record				
Yes	12	4	0.91 (0.01–2.37)	0.93
No	320	88	1	
Peak body temperature, °C				
<39	15	1	1	
39–40	167	21	2.21 (0.72–6.80)	0.17
40–41	125	45	3.15 (1.06–9.36)	0.04
41	18	18	11.25 (3.34–37.86)	<0.001
Symptoms				
Convulsion				
Yes	290	76	1.19 (0.66–2.15)	0.56
No	44	14	1	
Mucosal disease				
Yes	49	4	0.49 (0.15–1.25)	0.12
No	305	86	1	
Arthralgia				
Yes	8	1	0.47 (0.08–2.62)	0.45
No	320	92	1	
Diarrhea				
Yes	24	12	2.23 (1.05–4.72)	0.04
No	310	81	1	
Blood examinations AST, IU/L				
<100	224	22	1	
100–500	53	28	5.45 (2.89–10.27)	<0.001
500	19	32	17.38 (8.49–35.59)	<0.001
Creatine phosphokinase, IU/L				
<200	189	33	1	
200–1000	65	22	1.94 (1.06–3.56)	0.03
1000	16	20	7.16 (3.37–15.22)	<0.001
Hct, g/dL				
16	25	48	10.79 (5.87–19.85)	<0.001
16	256	35	1	
Blood glucose, mg/dL				
70	2	6	34.71 (6.40–188.29)	<0.001
70–150	162	11	1	
150	107	32	6.28 (3.33–11.84)	<0.001
Urine test				
Normal	142	11	1	
Hematuria or proteinuria	51	18	9.65 (4.87–19.10)	<0.001
Brain CT findings				
Normal	154	16	1	
Edema or diffuse low densities	132	62	4.24 (2.34–7.70)	<0.001
Medication				
Acetaminophen				
Yes	129	41	1.09 (0.56–1.58)	0.89
No	112	17	1	
Diclofenac acid				
Yes	89	4	1.08 (1.55–7.50)	<0.001
No	278	41	1	
Mefenamic acid				
Yes			2.14 (1.09–4.13)	0.04

442 patients with influenza-associated encephalopathy

Characteristics	Missing data
Age	0
Sex	0
Virus types	28
Allergy	0
Flu vaccination record	21
Peak body temperature	69
Diarrhea	12
AST	61
Creatinine phosphokinase	97
Platelet	85
Blood sugar	96
Urine test	144
Brain CT findings	75
Acetaminophen	47
Diclofenac sodium	47
Mephenamic acid	47

184 patients with complete data for 16 variables were included in multivariate analysis

FIGURE 1. Flow chart of patient selection. A total of 442 patients with influenza-associated encephalopathy were reduced to 184 patients because of missing data points in the variables. Variables with missing data are shown with the number of missing data points. AST indicates aspartate aminotransferase; CT, computed tomography.

placed patients with allergies in the good prognosis group in univariate analysis. However, allergy history did not have a significant effect in multivariate analysis, possibly because of control of confounding.

DISCUSSION

An outbreak of encephalopathy suspected to have been caused by influenza infection prompted a national survey of influenza-associated encephalopathy at all hospitals and pediatric clinics in Japan, as well as this analysis of 442 cases. To our knowledge, this is the first study on the prognostic factors of influenza-associated encephalopathy. The mortality rate was as high as 30% without treatment[1] Therefore, for the administration of intensive care, it is important to identify the factors that affect its prognosis. Using multivariate analysis we identified several factors that were related to the poor prognosis of this disease.

A severely elevated transaminase level, thrombocytopenia, and hematuria or proteinuria were associated with an unfavorable outcome in influenza-associated encephalopathy. Although the pathogenesis of this disease is still unclear, several reports[11] have suggested that it involves cytokines, such as soluble tumor necrosis factor receptor 1, interleukin (IL)-1β, IL-6, IL-8 is measured serum factor α (TNF-α, IL-6 and IL-8). Nerves and Ivana-Behre: in reduced in analysis of the influenza-associated encephalopathy patients, ...

encephalopathy patients, suggesting the activation of macrophages and microglia cells by hypercytokinemia[11] A severely elevated transaminase level, thrombocytopenia, and hematuria or proteinuria may be associated with disseminated intravascular coagulopathy, multiple organ failure, and hemophagocytosis resulting from hypercytokinemia induced by this disease[3,10,11]

We also showed that hyperglycemia is a factor leading to poor prognosis. IL-6 may lead to increased cortisol levels, followed by a pronounced dose-dependent increase in blood glucose[15,16] Therefore, we postulated that the systemic hypercytokinemia in influenza-associated encephalopathy causes hyperglycemia and that the glucose levels reflect the degree of pathogenicity.

Hypoglycemia provided a significant P value of 0.05 in univariate analysis. However, this did not result in a significant difference in the multivariate analysis, which was probably because the number of patients with hypoglycemia in multivariate analysis was reduced from 8 to only 2 cases, or 1.1% of patients, because of missing data. Hypoglycemia is a symptom of Reye syndrome with a very poor prognosis[17,18] Medium-chain acyl-CoA dehydrogenase deficiency is the most common disorder of fatty acid β-oxidation, and occurs acutely in Reye's-like syndrome, which is often provoked by infection[19] Reye's-like syndrome is similar to influenza-associated encephalopathy in several of its symptoms, such as loss of consciousness, seizures, and increased aminotransferase levels[17,20] Therefore, we postulated that influenza-associated encephalopathy may include a metabolic disorder, such as medium-chain acyl-CoA dehydrogenase deficiency.

High-grade fever, particularly >41°C, showed a tendency toward being a prognostic factor in the multivariate analysis. Some patients with a poor outcome exhibit a mitochondrial β-oxidation disorder evoked by inactivated carnitine palmitoyltransferase II during high-grade fever in influenza-associated encephalopathy[21] Analysis of the genotypes and allele compositions of carnitine palmitoyltransferase II have revealed a thermolabile phenotype that occurs more frequently in influenza-associated encephalopathy patients than in healthy subjects[21] In addition, the use of the nonsalicylate antipyretic drug diclofenac to alleviate fever affected the prognosis of the disease, and the use of mefenamic acid tended to also influence the prognosis, whereas the use of acetaminophen was considered to have little effect. In May 2001, the Japanese Ministry of Health, Labor and Welfare banned the use of these antipyretic drugs to alleviate fever in influenza infection based on the data of the Collaborative Study Group on Influenza-Associated Encephalopathy[1] However, it is still unclear whether these drugs are related to the pathogenesis of influenza-associated encephalopathy. Shiga-like toxin II or Shiga-like toxin II-stimulated cytokines may change the brain penetration of diclofenac sodium and mefenamic acid and consequently increase the risk of the drugs having the contradictory central systemic side effects.

We did not find a significant correlation between influenza-associated encephalopathy and ...

TABLE 2. Characteristics of Admission and Multivariate Analysis of Prognostic Factors in the 184 Patients Included in This Study Between 1998 and 2002

Variable	No. Patients		Odds Ratio (95% CI)	*P*
	Survival (n = 149)	Death (n = 35)		
Age (yr)				
<1	11	1	1	
1–6	115	31	1.12 (0.05–26.16)	0.94
6–15	23	3	0.09 (0.001–6.24)	0.26
Sex				
Male	76	12	0.40 (0.11–1.74)	0.27
Female	73	23	1	
Virus types				
Type A	135	29	0.56 (0.06–5.78)	0.63
Type B	14	6	1	
Past history				
Allergy				
Yes	8	1	1.10 (0.06–21.19)	0.91
No	141	34	1	
Flu vaccination record				
Yes	7	1	0.20 (0.02–5.57)	0.41
No	142	34	1	
Peak body temperature (°C)				
<39	22	1	1	
39–40	59	9	11.72 (0.31–442.39)	0.18
40–41	60	18	15.65 (0.42–577.88)	0.14
>41	8	7	42.61 (0.98–1851.87)	0.05
Symptom				
Diarrhea				
Yes	9	5	2.28 (0.26–20.25)	0.46
No	140	30	1	
Blood examination AST (IU/L)				
<100	103	7	1	
100–500	33	8	1.76 (0.40–7.64)	0.45
>500	**13**	**20**	**7.88 (1.15–54.00)**	**0.04**
Creatine phosphokinase (IU/L)				
<200	101	15	1	
200–1000	37	9	1.03 (0.20–5.30)	0.97
>1000	11	11	1.08 (0.13–9.16)	0.94
Platelet (×10⁴/μL)				
<10	16	20	3.79 (0.55–26.21)	0.18
≥10	133	15	1	
Blood glucose (mg/dL)				
<50	1	1	28.70 (0.35–2372.08)	0.14
50–150	83	5	1	
>150	**65**	**29**	**4.73 (1.10–20.30)**	**0.04**
Urine test				
Normal	108	10	1	
Hematuria or proteinuria	**41**	**25**	**7.96 (1.76–35.92)**	**0.01**
Brain CT findings				
Normal	85	6	1	
Edema, low density area, hemorrhage	64	29	2.59 (0.68–9.90)	0.17
Medication				
Acetaminophen				
Yes	94	21	1.46 (0.38–5.56)	0.58
No	55	14	1	
Diclofenac sodium				
Yes	**8**	**7**	**16.34 (1.27–210.18)**	**0.03**
No	141	28	1	
Mefenamic acid				
Yes	2	5	0.11 ([illegible]–12.[illegible])	[illegible]
No	147	30	1	

[illegible]

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

and hypothermia therapy were proposed by the Collaborative Study Group on Influenza-Associated Encephalopathy, and further studies to improve influenza-associated encephalopathy prognosis via therapy are currently underway.

In conclusion, we identified several factors related to the poor prognosis of influenza-associated encephalopathy. Use of diclofenac sodium was the causal factor of poor prognosis. The other factors seem to reflect systemic hypercytokinemia, which is thought to play a role in the pathogenesis of the disease. However, all of these factors (with the exception of the use of diclofenac sodium) may be secondary to the disease process because they are seen in subjects who are moribund from a number of causes. Although these factors cannot be used to make an early diagnosis, our results have 2 major implications: the prognostic factors that we identified are easy to examine clinically, and these factors are important for the administration of intensive care in cases of influenza-associated encephalopathy.

REFERENCES

1. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis*. 2002;35:512–517.
2. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med*. 2005;353:2559–2567.
3. Steininger C, Popow-Kraupp T, Laferl H, et al. Acute encephalopathy associated with influenza A virus infection. *Clin Infect Dis*. 2003;36:567–574.
4. Hall SM. Reye's syndrome and aspirin: a review. *J R Soc Med*. 1986;79:596–598.
5. Belay ED, Bresee JS, Holman RC, et al. Reye's syndrome in the United States from 1981 through 1997. *N Engl J Med*. 1999;340:1377–1382.
6. Kawashima H, Togashi T, Yamanaka G, et al. Efficacy of plasma exchange and methylprednisolone pulse therapy on influenza-associated encephalopathy. *J Infect*. 2005;51:E53–E56.
7. Munakata M, Kato R, Yokoyama H, et al. Combined therapy with hypothermia and anticytokine agents in influenza A encephalopathy. *Brain Dev*. 2000;22:373–377.
8. Ichiyama T, Morishima T, Isumi H, et al. Analysis of cytokine levels and NF-kappaB activation in peripheral blood mononuclear cells in influenza virus-associated encephalopathy. *Cytokine*. 2004;27:31–37.
9. Ito Y, Ichiyama T, Kimura H, et al. Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. *J Med Virol*. 1999;58:420–425.
10. Kawada J, Kimura H, Ito Y, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. *J Infect Dis*. 2003;188:690–698.
11. Nunoi H, Mercado MR, Mizukami T, et al. Apoptosis under hypercytokinemia is a possible pathogenesis in influenza-associated encephalopathy. *Pediatr Int*. 2005;47:175–179.
12. Ichiyama T, Isumi H, Ozawa H, et al. Cerebrospinal fluid and serum levels of cytokines and soluble tumor necrosis factor receptor in influenza virus-associated encephalopathy. *Scand J Infect Dis*. 2003;35:59–61.
13. Yokota S, Imagawa T, Miyamae T, et al. Hypothetical pathophysiology of acute encephalopathy and encephalitis related to influenza virus infection and hypothermia therapy. *Pediatr Int*. 2000;42:197–203.
14. Watanabe T, Okazaki E, Shibuya H. Influenza A virus-associated encephalopathy with haemophagocytic syndrome. *Eur J Pediatr*. 2003;162:799–800.
15. Harnish MJ, Lange T, Dimitrov S, et al. Differential regulation of human blood glucose level by interleukin-2 and -6. *Exp Clin Endocrinol Diabetes*. 2005;113:43–48.
16. Tsigos C, Papanicolaou DA, Kyrou I, et al. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. *J Clin Endocrinol Metab*. 1997;82:4167–4170.
17. Glasgow JF, Middleton B. Reye syndrome—insights on causation and prognosis. *Arch Dis Child*. 2001;85:351–353.
18. Maheady DC. Reye's syndrome: review and update. *J Pediatr Health Care*. 1989;3:246–250.
19. Bzduch V, Behulova D, Salingova A, et al. Serum free carnitine in medium chain acyl-CoA dehydrogenase deficiency. *Bratisl Lek Listy*. 2003;104:405–407.
20. Bzduch V, Behulova D, Lehnert W, et al. Metabolic cause of Reye-like syndrome. *Bratisl Lek Listy*. 2001;102:427–429.
21. Chen Y, Mizuguchi H, Yao D, et al. Thermolabile phenotype of carnitine palmitoyltransferase II variations as a predisposing factor for influenza-associated encephalopathy. *FEBS Lett*. 2005;579:2040–2044.
22. Fukuda M, Kitaichi K, Abe F, et al. Altered brain penetration of diclofenac and mefenamic acid, but not acetaminophen, in Shiga-like toxin II-treated mice. *J Pharmacol Sci*. 2005;97:525–532. AQ:2

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

日本外来小児科学会予防接種委員会

麻しん及び風しんの定期予防接種の接種体制に関する全国自治体への調査報告

日本外来小児科学会予防接種委員会

藤岡　雅司　　永井　崇雄　　落合　　仁

崎山　　弘　　田原　卓浩　　寺田　喜平

宮崎　千明　　横田俊一郎　　吉川　哲史

背　景

平成17年7月29日に予防接種関連法令が改正され，平成18年4月1日から麻しん及び風しんの定期の予防接種の方法が大幅に変更された．定期接種として使用できるワクチンが弱毒生麻しん風しん混合（以下，MR）ワクチンだけと定められた．そして，定期の予防接種の対象年齢が1歳と就学前年の各々1年間の計2年間に短縮された．また，制度変更に伴う経過措置が設定されなかった．その結果，新制度の下では，一方の接種済み者や罹患者は，もう一方の定期の予防接種を受けられなくなることや，2歳以上の未接種者は就学前まで放置されることなど，法令改正にかかる問題点の指摘が関連学会や関連団体などから相次いだ．結局は，改正法令施行から2か月後の平成18年6月2日に関連法令の再改正が行われ，一部の問題点は解決した．しかし，改正法令が公布されてからの10か月間，定期接種の実務を行う市町村や医療関係者は厚生労働省の対応に翻弄され続けた．

目　的

今回の一連の麻しん及び風しんの定期接種に関わる予防接種関連法令の改正によって，定期接種の実施主体である市町村や地区の医師会，小児科医会等は，その対応で混乱した．すなわち，当初の改正法令の公布から施行までの経過と，異例の短期間で法令の再改正が行われたための二重の混乱である．

今回のアンケートは，このような経過の中で，定期接種の実施主体である市町村の対応を調査するために実施した．日本外来小児科学会では一昨年にBCGの制度変更についての全国調査も行った．BCG調査で指摘した問題点も参考に，今回の麻しん及び風しんの定期接種についての一連の混乱の原因も検討した．

方　法

全国すべての都道府県及び政令指定都市の予防接種担当課に対しアンケート調査を行った．都道府県に対しては市町村の対応を集計した回答を依頼した．質問の内容は，平成18年8月時点での麻しん及び風しんの定期予防接種の実施体制（接種方式，接種時期の制限や実費徴収の有無），未接種者への対応と健康被害への補償体制である．また，今回の法令改正に対する地方自治体の立場での意見も自由記載で依頼した．回答は久留米大学医療センター小児科で回収して集計し，日本外来小児科学会予防接種委員会において結果の分析を行った．

結　果

1）回収率と市町村数の内訳

47都道府県と15政令指定都市の合計62自治体にアンケートを送付し，36府県と14政令指定都市の合計50自治体から回答が得られた．回収率は80.6％であった．平成18年8月1日現在の全国の市町村数は1,819で，集計した市町村の総数は1,310（72.0％）であった．

図1に回答した市町村の内訳を示す．このうち政令指定都市と中核市・特例市を合わせて大規模市，その他の市を小規模市，町と村を合わせて町村部とすると，それぞれ49（3.7％），564（43.1％），697（53.2％）となった．残念ながら，今回は東京都から回答が得られなかったため，特別区は集計に含まれていない．

2）接種方式について

平成18年度の麻しん及び風しんの定期予防接種の接種方式は，回答のあった1,269市町村の中で，1,120（88.3％）が個別，76（6.0％）が集団，66（5.2％）が個

図1　回答市町村内訳