



Recent practice patterns in diagnostic procedures anticonvulsants, and antibiotics for children hospitalized with febrile seizure



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ABSTRACT

Purpose This study investigated clinical practice patterns for admissions due to FS at a national level.

Method Discharge records were extracted for patients with FS aged < 6 years for the years 2010–16 using national inpatient database in Japan. We ascertained antiepileptic drug use, diagnostic procedures, healthcare costs, and length of hospital stays (LOS), using mixed effect linear or logistic regression models. We also investigated correlations between performance of lumbar puncture (LP), and use of head computed tomography (CT) and antibiotics.

Results We identified a total of 94,452 eligible patients. Hospitalization costs and LOS in days decreased from 19,027 JPY and 4.6 days in 2010 to 18,753 JPY and 4.1 days in 2016. Phenytoin use decreased from 1.6% in 2010 to 0.5% in 2016, whereas fosphenytoin use increased from 0% in 2010 to 6.7% in 2016. Decreasing trends were observed in CT use (from 32.8% to 16.9%) and LP performance (16.9% to 13.5%). For the analyses at hospital levels, CT use and LP performance was positively correlated ($r = 0.63$). No correlations were observed between total and extremely broad-spectrum antibiotic use and CT use or LP performance in hospitals without cases of intensive care. Wide variations were observed across hospitals for performance of LP (0%–88%), use of CT (0%–84%) and antibiotics (10%–99%).

Conclusion We provided novel insights into the current practice patterns for children with FS at individual levels, and delineated wide variations of LP, CT, and antibiotic use for the practices at hospital levels.

1. Introduction

Febrile seizure (FS) is the most common type of seizure observed in children. FS is characterized by episodes of convulsions that occur in association with fever in children aged between 3 months and 6 years without a central nervous system infections or electrolyte imbalance [1–5]. FS is believed to be a benign seizure syndrome, and is distinct from other neurologic disorders.

Diagnoses and initial managements of FS are aimed to exclude acute symptomatic seizure other than FS and early cessation of seizure with antiepileptic drugs (AEDs) [3,5]. The exclusions of acute symptomatic seizure are made based on clinical characteristics and diagnostic procedures such as lumbar punctures (LP) and radiologic studies such as

computed tomography (CT) and magnetic resonance imaging (MRI). The management of FS consists of AEDs use, close observations, and sometimes antibiotics use for comorbid infectious diseases. Although several studies have revealed the diagnostic practice patterns (LP and CT) and their variabilities, these studies were limited due to relatively small sample sizes, underestimation of the procedures, and lack of generalizability [6–9]. Furthermore, no studies have revealed treatment patterns in terms of AED and antibiotic use, their relevance to diagnostic procedures, and healthcare costs at a national level.

To address the gaps in knowledge, this study investigated recent diagnostic and treatment patterns of FS using national inpatient database in Japan.

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2. Methods

2.1. Study population and participation

We extracted hospital discharge records of pediatric inpatients between 6 months and 6 years of age with FS using the Diagnosis Procedure Combination inpatient database between July 1, 2010 and March 31, 2016. The details of the database have been described elsewhere [10]. Briefly, the database was collected from more than 1000 hospitals, and it covers up to 55% of all inpatient admissions to acute-care hospitals in Japan. The database has hospital discharge and administrative claims data for approximately 7 million inpatients per year. It includes information on the following: the patient's main diagnosis; pre-existing comorbidities at admission; complications during hospitalization; the patient's age, sex, and body weight; dates when procedures and treatments were performed. Approval for the present study was obtained from the Institutional Review Board at The University of Tokyo. The Board waived the requirement for informed consent because of the anonymous nature of the data.

Hospitalizations with FS were identified using the International Classification of Diseases, Tenth Revision code (ICD-10 code, R56.0) as the main diagnosis at admission. We included only patients aged between 6 months and 6 years to maximize the diagnostic accuracy. We excluded patients with diagnoses of meningitis, encephalitis/encephalopathy, afebrile seizure, and convulsion with mild gastroenteritis. Patients with chronic medical conditions were also excluded to avoid misclassifications of acute symptomatic seizure. Chronic medical conditions were defined according to the pediatric complex chronic conditions classification system version 2 [11].

2.2. Measurements of variables

Patient characteristics included age, sex, weight in kg, season and year of admission, ambulance use, hospital type (academic or non-academic), and need for intensive care.

The outcomes of interest were diagnostic procedures, AEDs and antibiotic use, total hospitalization costs, and total length of hospital stay in days. Diagnostic procedures consisted of LP, CT, and MRI. AEDs include benzodiazepine, phenytoin, fosphenytoin, barbiturate, ketamine, and propofol. Antibiotic use was estimated using days of therapy (DOT) per inpatient day, and we calculated DOTs per inpatient day for total antibiotics and broad-spectrum antibiotics. We defined 4th generation cephalosporin, carbapenems, quinolone, and piperacillin, and piperacillin-tazobactam as extremely broad-spectrum antibiotics.

2.3. Statistical analyses

We investigated the annual trends in total hospitalization costs, and LOS, and practice and treatment patterns from 2010 to 2016. To evaluate the trends, we constructed multivariable mixed effects logistic or linear regression models that contained year of admission as a continuous variable. All models included fixed effects for patient characteristics (age, sex, ambulance use, and season of admission) and random effects for hospitals.

Then, we selected 277 hospitals that had at least 10 FS patients per year to ascertain the correlations between the proportions of LP, CT use, and total and broad-spectrum antibiotic use. We conducted Pearson's correlation coefficients separately based on the presence of patients admitted to intensive care unit (ICU) in the hospitals because hospitals with patients admitted to ICU may have had different severity of FS from those without. Statistical significance was two-sided $P < 0.05$ for all analyses. All data were analyzed using STATA software version 14.2 (StataCorp LP, TX, USA).

Table 1

Trends in baseline characteristics for FS-associated hospitalizations from 2010 to 2016.

	2010	2011	2012	2013	2014	2015	2016
Admission, N	7266	14,255	15,832	16,231	17,890	17,764	5214
Age, mean (SD)	2.2 (0.01)	2.28 (0.01)	2.29 (0.01)	2.25 (0.01)	2.25 (0.01)	2.23 (0.01)	2.43 (0.02)
Female, N (%)	3558 (49.0)	6937 (48.7)	7283 (46.0)	7133 (43.9)	7474 (41.8)	7051 (39.7)	1956 (37.5)
Male, N (%)	3708 (51.0)	7318 (51.3)	8549 (54.0)	9098 (56.1)	10416 (58.2)	10713 (60.3)	3258 (62.5)
Ambulance use, N (%)	3696 (50.9)	7297 (51.2)	8521 (53.8)	9077 (55.9%)	10376 (58.0)	10685 (60.1)	3253 (62.4)
Academic hospital, N (%)	664 (9.1)	1596 (11.2)	1559 (9.8)	1575 (9.7)	1762 (9.8)	1748 (9.8)	542 (10.4)
Spring, N (%)	–	4159 (29.2)	4132 (26.1)	4372 (26.9)	4683 (26.2)	4409 (24.8)	1574 (30.2)
Summer, N (%)	2674 (36.8)	3794 (26.6)	4381 (27.7)	4546 (28.0)	5227 (29.2)	5131 (28.9)	–
Fall, N (%)	3109 (42.8)	2426 (17.0)	3287 (20.8)	3142 (19.4)	3637 (20.3)	3603 (20.3)	–
Winter, N (%)	1483 (20.4)	3876 (27.2)	4032 (25.5)	4171 (25.7)	4343 (24.3)	4621 (26.0)	3640 (69.8)

3. Results

We identified a total of 94,452 children who were hospitalized with FS. Table 1 summarizes the baseline characteristics of children with FS during 2010–2016. The mean age for hospitalized children with FS was 2.2–2.4 years with slight male predominance. The proportions of ambulance use ranged between 50.9%–62.4%. The proportions of academic hospital admissions varied between 9%–11%.

Table 2 shows the trends in healthcare costs, length of stay, and patterns of treatment and diagnostic procedures. Decreasing trends were observed in total hospitalization costs (from 19,027 JPY in 2010 to 18,753 JPY in 2016) and LOS (from 4.6 days in 2010 to 4.1 days in 2016). Approximately, 70% of FS inpatients received either rectal suppository or intravenous benzodiazepines during 2010–2016. Phenytoin use decreased from 1.6% in 2010 to 0.5% in 2016, whereas fosphenytoin use increased from 0% in 2010 to 6.7% in 2016 ($P_{trend} < 0.001$). Barbiturate, ketamine, and propofol use did not change during 2010–2016.

CT use showed a decreasing trend from 32.8% in 2012 to 28.8% in 2016 ($P_{trend} < 0.001$). In contrast, MRI use showed slight increasing trend from 4.9% in 2010 to 6.6% in 2016 ($P_{trend} = 0.01$). Antibiotic use had significant downward trend from 2.2 DOTs per inpatient-day in 2010 to 1.4 DOTs per inpatient-day in 2016 ($P_{trend} < 0.001$).

Fig. 1 demonstrates the correlation between proportions of LP and CT use by hospital types. Moderate positive correlations between LP and CT use were observed in hospitals with ICU cases ($r = 0.63$; $p < 0.001$) and those without ($r = 0.63$; $p < 0.001$).

Fig. 2a and 2b depict correlations between CT and total or broad-spectrum antibiotic use. Both hospital types did not have significant correlations between CT and total antibiotic use. Correlation between CT and broad-spectrum antibiotic use was close to zero in hospitals without ICU cases ($r = -0.15$; $p = 0.046$) and in hospitals with ICU cases ($r = 0.04$; $p = 0.68$).

Fig. 3a and 3b depict the correlations between LP and total or broad-spectrum antibiotic use. Correlations were close to zero in hospitals without ICU cases between LP and total antibiotic use ($r = -0.20$; $p = 0.008$) and between LP and broad-spectrum antibiotic use ($r = -0.16$; $p = 0.028$). We found no significant correlations between LP and total or broad-spectrum antibiotic use in the hospitals with ICU cases.

Table 2
Trends in hospital utilizations and practice patterns from 2010 to 2016.

	2010	2011	2012	2013	2014	2015	2016	<i>P</i> trend
Admission, N	7266	14,255	15,832	16,231	17,890	17,764	5214	
Hospitalization cost in JPY, mean (SD ¹)	19,027 (298.9)	18,865 (101.9)	19,042 (90.6)	19,145 (91.9)	19,351 (134.3)	19,703 (108.7)	18,753 (138.1)	0.005
Length of stay, days (SD)	4.61 (0.05)	4.58 (0.02)	4.47 (0.02)	4.43 (0.02)	4.39 (0.02)	4.41 (0.02)	4.12 (0.03)	< 0.001
Benzodiazepine sup., N (%)	3887 (53.5)	9130 (64.0)	10421 (65.8)	10443 (64.3)	11158 (62.4)	10636 (59.9)	2954 (56.7)	0.09
Benzodiazepine iv, N (%)	996 (13.7)	2277 (15.9)	2838 (17.9)	3021 (18.6)	3224 (18.0)	3207 (18.0)	871 (16.7)	< 0.001
Phenytoin, N (%)	117 (1.6)	263 (1.8)	215 (1.4)	118 (0.7)	69 (0.4)	84 (0.5)	28 (0.5)	< 0.001
Fosphenytoin, N (%)	0 (0)	0 (0)	145 (0.9)	444 (2.7)	691 (3.9)	989 (5.6)	349 (6.7)	< 0.001
Barbiturate, N (%)	353 (4.9)	903 (6.3)	1032 (6.5)	1004 (6.2)	1110 (6.2)	1094 (6.2)	277 (5.3)	0.55
Ketamine, N (%)	43 (0.6)	85 (0.6)	115 (0.7)	99 (0.6)	148 (0.8)	121 (0.7)	29 (0.6)	0.08
Propofol, N (%)	9 (0.1)	25 (0.2)	41 (0.3)	32 (0.2)	22 (0.1)	18 (0.1)	6 (0.1)	–
Lumber puncture, N (%)	1036 (14.3)	2487 (17.4)	2683 (16.9)	2751 (16.9)	2749 (15.4)	2691 (15.1)	702 (13.5)	< 0.001
CT ² , N (%)	1937 (26.7)	4508 (31.6)	5190 (32.8)	5039 (31.0)	5088 (28.4)	5032 (28.3)	1504 (28.8)	< 0.001
MRI ³ , N (%)	356 (4.9)	909 (6.4)	1133 (7.2)	1158 (7.1)	1248 (7.0)	1202 (6.8)	345 (6.6)	0.01
Need for intensive care, N (%)	14 (0.2)	44 (0.3)	57 (0.4)	57 (0.4)	70 (0.4)	78 (0.4)	17 (0.3)	0.25
DOTs per inpatient-day ⁴ (SD)	2.17 (0.04)	2.41 (0.03)	2.45 (0.03)	2.26 (0.03)	2.16 (0.04)	2.06 (0.02)	1.39 (0.03)	< 0.001

* 1 SD, standard deviation; *2 CT, computed tomography; *3 MRI, magnetic resonance imaging; *4 DOTs, days of antimicrobial therapy.

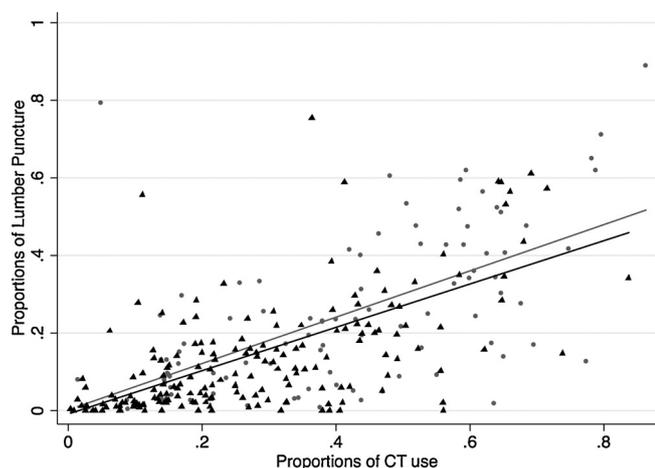


Fig. 1. The correlations between use of computed tomography and performance of lumbar puncture. Black triangles and solid line represents hospitals with admissions to intensive care unit (ICU). Gray circles and solid line shows hospitals without admissions to ICU.

4. Discussion

The present study demonstrates the most recent trends in practice patterns and hospital utilizations for pediatric inpatients due to FS in Japan for the years 2010–2016. Overall, hospitalization costs and LOS decreased over the period, and patterns in AEDs and diagnostic procedures changed especially for phenytoin, fosphenytoin, and CT/MRI use. LP and CT use are correlated at hospital levels. To the best of our knowledge, this is the first study that investigated the clinical practice patterns for FS at a national level.

Increasing healthcare expenditure is one of the important concerns for sustainable healthcare among most developed countries. For example, in the US, the average healthcare costs of a child hospitalized

with FS markedly increased from \$2870 in 2003 to \$3792 in 2012, similar to hospitalizations with other common pediatric disorders [1,12–16]. In contrast, we found a slight decreasing trend in hospitalization costs over the period. The trend may have reflected a decrease in LOS and overall natural trends in pediatric inpatients in Japan. Indeed, similar decreasing patterns were observed in other pediatric disorders, such as immune thrombocytopenia, and respiratory infections such as *Mycoplasma pneumoniae* and influenza virus [17–19].

Our study revealed a constantly common prescriptions of benzodiazepine suppository and some changes in AED prescription patterns in terms of a slight increase in intravenous benzodiazepine use, a decrease in phenytoin use, and a corresponding increase in fosphenytoin use. First, a diazepam suppository was by far the most commonly used for inpatients with FS in Japan. This is because most physicians in Japan expect the effects of slowly absorbed benzodiazepine suppository on preventing subsequent seizure recurrence [20]. Second, intravenous benzodiazepines slightly increased over the period. The trend may have reflected physicians’ preference, where most pediatric inpatients with FS have intravenous line at admissions. Third, a decrease in phenytoin use and a corresponding increase in fosphenytoin use can reflect the approval of fosphenytoin to the universal healthcare coverage in 2012 in Japan. Physicians preferred to use fosphenytoin because of its proven efficacy and increased safety compared with phenytoin, which was notorious for severe infusion reaction and adverse effects such as cardiac arrhythmia and thrombophlebitis.

We observed decreasing trends in LP and CT use over the study period. Similar trends were observed in a previous national survey in the US showing that LP was performed for 25.8% of FS patients with a decreasing trend from 2007 to 2014 [8,9]. These similar trends across different nations may have reflected physicians’ questions against routine performance of LP because the incidence of CNS infections among FS encounters were estimated to be very low at 0.3%–0.8% after the introduction of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines [7,8]. Another study in a tertiary center in the US showed head CT was performed approximately 28% of patients with FS,

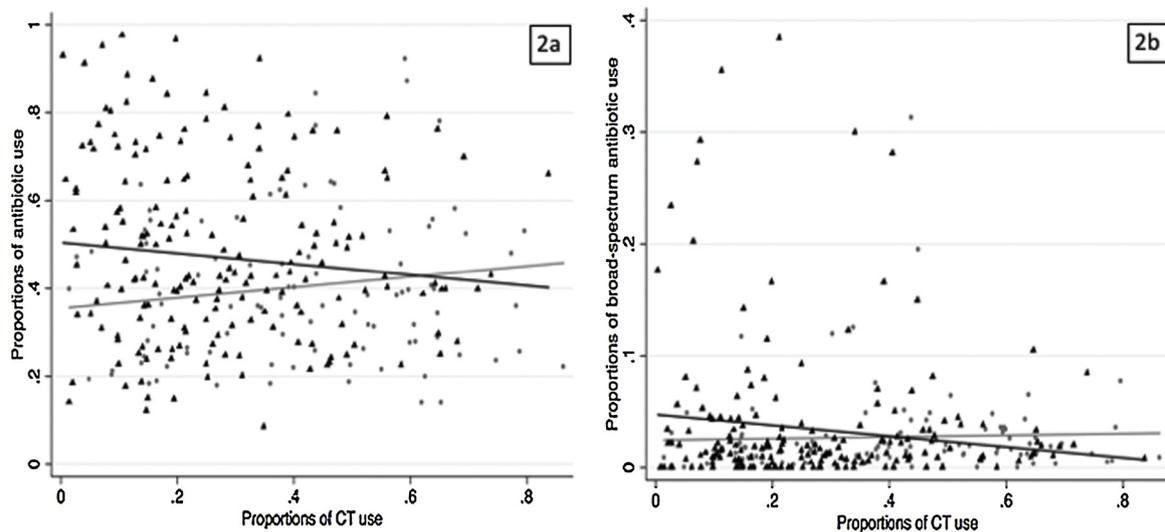


Fig. 2. Fig. 2a demonstrates the correlations between use of computed tomography (CT) and use of total antibiotics. Fig. 2b. The correlations between use of computed tomography (CT) and use of extremely broad-spectrum antibiotics. Black triangles and solid line represents hospitals with admissions to intensive care unit (ICU). Gray circles and solid line shows hospitals without admissions to ICU.

which was similar to our findings [9]. The decreasing trend of CT use may have been due to physicians concerns about the subsequent risk of leukemia and brain tumors reported in 2012 [21].

Finally, we observed positive correlations between CT use and LP performance at hospital levels. The findings could be explained by the standard procedures at hospital levels that physicians took head CT scans before performing LP in order to evaluate the signs of increased intracranial pressure due to any causes including meningoencephalitis, which is the most frightening cause of acute symptomatic seizure with fever. However, the variations of these procedures at the hospital levels were very wide, ranging from 0% to 80% for both LP and CT. We assume that some hospitals performed unnecessary LP and CT almost routinely, suggesting promotions of standardized practice for FS inpatients to these hospitals.

In addition, we observed no correlation between diagnostic procedures (LP, CT) and total or extremely broad-spectrum antibiotic use among hospitals without ICU cases with wide variations of antibiotic use. These findings indicate that several hospitals used antibiotics almost routinely for their FS inpatients. However, the patterns could not

be justifiable since some hospitals used extremely broad-spectrum antibiotics even though the rational for using 4th generation cephalosporins, carbapenems, and quinolones are limited for inpatients with FS.

There are several limitations to our study. The number of FS-associated hospitalization and comorbid medical conditions may have been under-estimated because of possible underreporting or misclassification. The detailed clinical presentation, physical examination, laboratory data, and results of the imaging studies were unavailable in the database. Inclusion for only hospitals with > 10 patients per year may have led to the selection bias. A unique feature and strength of this study was the use of a national inpatient database. Using this database, we were able to calculate robust national estimates of clinical practice patterns for children hospitalized with FS in the entire Japan.

In summary, we provided novel insights into the current clinical practice patterns of children with FS. Decreasing trends in healthcare costs, LP, CT, and antibiotic use were observed, but the variations in practice patterns were still wide at hospital levels. We believe our investigations could provide useful information for promoting further standardized practices of FS.

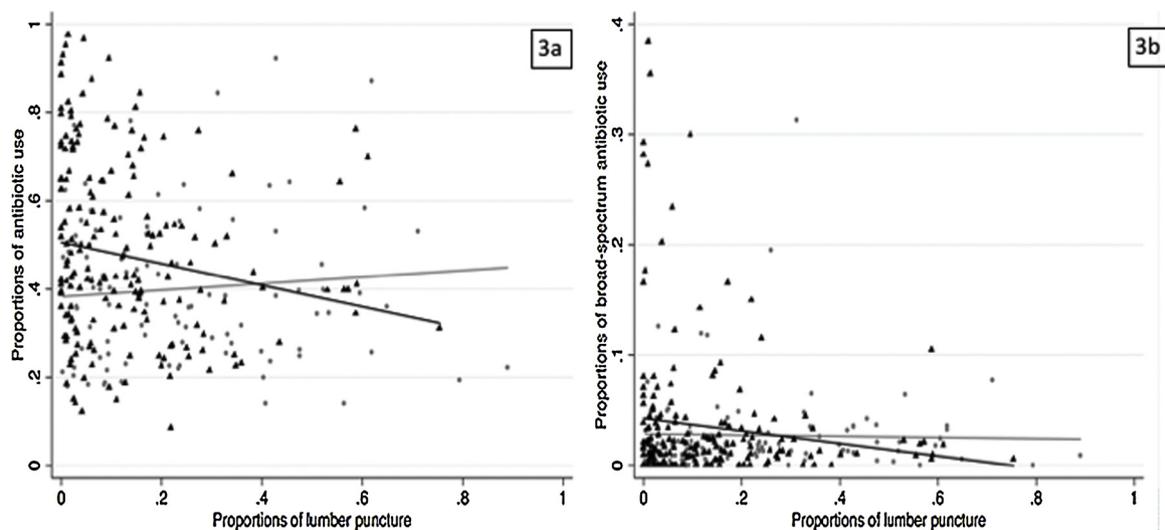


Fig. 3. Fig. 3a demonstrates the correlations between performance of lumbar puncture and use of total antibiotics. Fig. 3b. The correlations between performance of lumbar puncture and use of extremely broad-spectrum antibiotics. Black triangles and solid line represents hospitals with admissions to intensive care unit (ICU). Gray circles and solid line shows hospitals without admissions to ICU.

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Potential conflict of interest

The authors have no conflict of interest relevant to this article to disclose.

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