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Original article

Incidence of infantile spinal muscular atrophy on Shikoku Island of Japan

Kentaro Okamoto [a,b,*], Mitsumasa Fukuda [a,c], Isao Saito [d], Risako Urate [e], Satoshi Maniwa [f], Daisuke Usui [g], Takahiro Motoki [a], Toshihiro Jogamoto [a], Kaori Aibara [a], Takatoshi Hosokawa [h,i], Yukihiko Konishi [j], Reiko Arakawa [k], Kenji Mori [l], Eiichi Ishii [a], Kayoko Saito [k], Hisahide Nishio [m,n]

[a] *Department of Pediatrics, Ehime University Graduate School of Medicine, Ehime, Japan*
[b] *Department of Pediatrics, Ehime Prefectural Imabari Hospital, Ehime, Japan*
[c] *Department of Neuropediatrics, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*
[d] *Department of Community Health Systems Nursing, Ehime University Graduate School of Medicine, Ehime, Japan*
[e] *School of Medicine, Ehime University, Ehime, Japan*
[f] *Department of Pediatrics, Matsuyama Red Cross Hospital, Ehime, Japan*
[g] *Department of Pediatrics, Tano Hospital, Kochi, Japan*
[h] *Department of Pediatrics, Hosogi Hospital, Kochi, Japan*
[i] *Department of Pediatrics, Kochi Medical School, Kochi, Japan*
[j] *Department of Pediatrics, Faculty of Medicine, Kagawa University, Kagawa, Japan*
[k] *Institute of Medical Genetics, Tokyo Women's Medical University, Tokyo, Japan*
[l] *Department of Child Health & Nursing, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan*
[m] *Department of Occupational Therapy, Faculty of Rehabilitation, Kobe Gakuin University, Hyogo, Japan*
[n] *Department of Community Medicine and Social Healthcare Science, Kobe University Graduate School of Medicine, Hyogo, Japan*

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Abstract

Background: Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by homozygous mutations in the *SMN1* gene. SMA has long been known to be the most common genetic cause of infant mortality. However, there have been no reports on the epidemiology of infantile SMA (types 1 and 2) based on genetic testing in Japan. In this study, we estimated the incidence of infantile SMA on Shikoku Island, which is a main island of Japan and consists of four prefectures: Ehime, Kagawa, Tokushima and Kochi.

Methods: A questionnaire was sent to 91 hospitals on Shikoku Island to investigate the number of SMA infants born from 2011 to 2015. A second questionnaire was then sent to confirm the diagnoses of SMA based on clinical and genetic features.

Results: Responses were received from all of the hospitals, and four patients were diagnosed with infantile SMA among 147,950 live births. We estimated the incidence of infantile SMA patients as 2.7 per 100,000 live births (95% confidence interval, 0.1–5.4). A comparison of the four prefectures indicated that the incidence of infantile SMA was significantly higher in Ehime Prefecture than in the other three prefectures; 5.6 per 100,000 live births (95% confidence interval, −0.7 to 11.9) in Ehime Prefecture and 1.1 per 100,000 live births (95% confidence interval, −1.0 to 3.1) in the other prefectures.

* Corresponding author at: Department of Pediatrics, Ehime Prefectural Imabari Hospital, 4-5-5 Ishii, Imabari, Ehime 794-0006, Japan.
E-mail address: kentaro206@gmail.com (K. Okamoto).

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Conclusion: We estimated the incidence of infantile SMA in an isolated area of Japan. For more precise determination of the incidence of infantile SMA, further studies that include neonatal screening will be needed.

Keywords: Spinal muscular atrophy (SMA); Infantile SMA; Incidence; Epidemiology; Japan

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that results from degeneration of motor neurons of the spinal cord and is incurable [1]. SMA is clinically divided into four subtypes [2]; type 1 (Werdnig-Hoffman disease; the most severe form with onset before 6 months of age, unable to sit unsupported), type 2 (the intermediate severity form with onset between 7 and 18 months of age, able to sit unsupported but unable to stand or walk unaided), type 3 (Kugelberg-Welander disease; mild form with onset after 18 months of age, able to stand and walk unaided) and type 4 (the mildest form with onset in adulthood).

Although SMA is rare, it is now recognized as the leading genetic cause of death of infants [1]. SMA type 1 is the most common type, and accounts for approximately 50% of patients diagnosed with SMA [2]. Classically, infants with SMA type 1 have onset of clinical signs before 6 months of age, never acquire the ability to sit unsupported, and, if no intervention is provided, generally do not survive beyond 2 years of age [2]. MacLeod et al. [3] reported five patients with SMA type 1, who presented with reduced fetal movements *in utero*, severe weakness at birth and short survival times. Thus, urgent care is required for patients with SMA type 1.

The gene responsible for SMA is survival motor neuron 1 gene (*SMN1*) [4]. More than 95% of SMA patients show a homozygous loss of *SMN1* [4,5] and the remainder show a deleterious mutation in *SMN1*. The *SMN2* gene is highly homologous to *SMN1*. *SMN2* is retained in all SMA patients and generates low levels of SMN protein but does not fully compensate for the mutated *SMN1* [6]. However, higher copy numbers of *SMN2* may compensate for the loss of *SMN1* to some degree [7,8]. In the majority of cases, disease severity is inversely correlated with *SMN2* gene copy number [6]. Genetic tests are now used worldwide for the diagnosis of SMA. Muscle biopsy and electroneuromyography were essential for SMA diagnosis before the discovery of *SMN1* [1,9], but these procedures have gradually been replaced by genetic tests [2,10].

Although SMA incidences were reported before the discovery of *SMN1*, these may not be accurate because the data may include different diseases with similar symptoms. Recent epidemiologic studies of SMA are therefore based on genetic tests (Table 1). Incidences of all subtypes of SMA were 5.0–11.9 per 100,000 live births [11,13–17]. The incidences of SMA type 1 were reported as 3.5–7.1 per 100,000 live births [11–14], and those of SMA type 2 were 2.1 and 1.2 per 100,000 live births [11,14].

In Japan, Imaizumi [18] reported the incidence for SMA type 1 using death certificate records from all of Japan between 1979 and 1996. According to this study, the incidence was 1.2 per 100,000 live births, which is much lower than previous studies, indicating that a very small number of patients were clinically diagnosed with SMA. There were no genetic tests of SMA during this period in Japan, and there are no reports on the incidence of SMA based on genetic testing in Japan. In this study, we conducted an epidemiologic study to

Table 1
Incidence of SMA (all types and type 1) based on genetic testing.

Country	Study period	SMA (all types)			SMA (type 1)			References
		Cases	Population	Incidence	Cases	Population	Incidence	
Sweden	1980–2006	45	531,746	8.5[a]	19	531,746	3.6	[11]
Estonia	1994–2003				9	129,832	6.9	[12]
Cuba	1996–2002	51	1,018,454	5.0	36[b]	1,018,454	3.5	[13]
Poland	1998–2005	304	2,963,783	10.3	209	2,963,783	7.1	[14]
Ohio, USA	no description	4	40,103	10.0[c]				[15]
Europe	2011–2015	3776	22,325,221	11.9[d]				[16]
Taiwan	2014–2016	7	120,267	5.8[c]				[17]
Japan	2011–2015				4	147,950	2.7	This study

[a] All patients were younger than 16 years old.
[b] Genetic testing was used for some diagnoses (25/36; 69%).
[c] Newborn screening.
[d] Median incidence of several countries in Europe.

determine the incidence of infantile SMA based on genetic testing in Shikoku Island of Japan. We defined here infantile SMA as SMA type 1 and type 2.

2. Materials and methods

2.1. Study population

Shikoku Island, where the incidence of infantile SMA was determined in this study, is one of the four major islands of Japan (Fig. 1). The population of Shikoku Island is approximately 4 million, while the total population in Japan is approximately 127 million. Because Shikoku Island is surrounded by sea and isolated from the other major islands, population movement into or out of Shikoku Island is relatively low. Shikoku Island consists of four prefectures: Ehime, Kagawa, Tokushima and Kochi. The populations of the prefectures in 2015 were approximately 1.4, 1.0, 0.8 and 0.7 million in Ehime, Kagawa, Tokushima and Kochi, respectively (Table 2).

2.2. Questionnaires and patients

To investigate the number of SMA patients who were born in Shikoku Island during the period of January 2011 to December 2015, a questionnaire was sent to all 91 hospital pediatric departments. The questionnaire asked whether the doctors saw any patients with SMA. A second questionnaire was then sent to the pediatric departments with SMA patients, asking for clinical information including birth year, sex, subtypes of SMA, results of *SMN1* and *SMN2* genetic testing, current motor function and respiratory condition with or without tracheostomy. Sample questionnaires are provided in the Supplementary material. Additional information was obtained directly from the aforementioned doctors. Informed consent was obtained from the

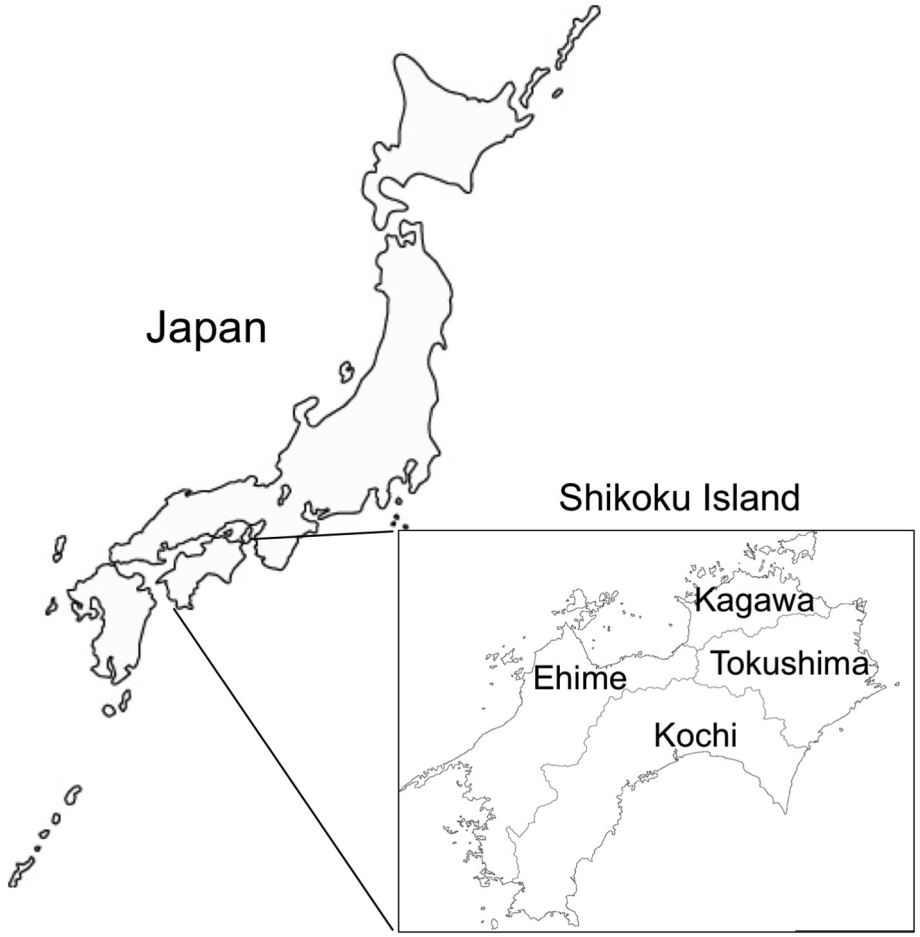

Fig. 1. Map of Japan and Shikoku Island. Shikoku Island, where the incidence of infantile spinal muscular atrophy was analyzed in this study, is one of the four major islands of Japan. Shikoku Island is surrounded by sea and isolated from the other major islands. Shikoku Island consists of four prefectures: Ehime, Kagawa, Tokushima and Kochi.

Table 2
Population and live birth numbers in the four prefectures of Shikoku Island in 2011–2015.

Population (×1000)						Live birth numbers					
Year	Ehime	Kagawa	Tokushima	Kochi	Total	Year	Ehime	Kagawa	Tokushima	Kochi	Total
2011	1424	992	780	758	3954	2011	11,329	8311	5914	5244	30,798
2012	1415	989	775	751	3930	2012	11,130	8161	5744	5266	30,301
2013	1406	985	769	743	3903	2013	10,696	8059	5666	5266	29,687
2014	1396	980	763	736	3875	2014	10,399	7745	5502	5015	28,661
2015	1385	976	756	728	3845	2015	10,146	7719	5586	5052	28,503

Total live birth numbers were 147,950.

parents of the confirmed SMA patients. This study was approved by the Institutional Review Board of Ehime University Hospital (approval number: 1610003).

2.3. Statistical analyses

Cumulative incidence was defined as the number of children diagnosed with SMA who were born between 2011 and 2015 in Shikoku Island in relation to the total number of live births in the study period. The incidence was defined as the number of new SMA patients in a year in the population, and was expressed as patient number per 100,000 live births. 95% confidence intervals were calculated based on the Poisson distribution. Population data were provided by the Statistics Bureau, Ministry of Internal Affairs and Communications of Japan. There were a total of 147,950 births in the period between January 2011 and December 2015 on Shikoku Island. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

2.4. Genetic tests

For cases 1–3, deletion of the *SMN1* gene was analyzed by the method of van der Steege et al. [19], which consists of PCR and restriction fragment length polymorphism (RFLP) analysis. Copy number of the *SMN2* gene was analyzed by the real-time PCR method of Tran et al. [20], in which the cystic fibrosis trans-membrane regulator (*CFTR*) gene is used as a reference gene for the relative quantification of copy number.

For case 4, copy numbers of *SMN1* and *SMN2* genes were determined by the multiplex ligation-dependent probe amplification (MLPA) method. For the MLPA analysis, the SALSA MLPA kit P021 (MRC-Holland, Amsterdam, the Netherlands) was used according to the manufacturer's instructions.

3. Results

3.1. Four patients with SMA type 1 found in the questionnaires

All 91 hospitals responded to the first questionnaire, and five patients with SMA-like disease were reported from four hospitals. All cases were carefully reviewed. An exclusion criterion of Prior's diagnostic testing strategy is the presence of two copies of *SMN1* [6]. Based on this exclusion criterion, one patient with two copies of *SMN1* was omitted from the study. Four patients with SMA type 1 were identified in this study, and their clinical features are summarized in Table 3. All four patients were born in Shikoku.

All cases presented with muscle weakness, respiratory distress and delay of motor development. The mean age of clinical onset was 4.5 months (minimum 1 month, maximum 9 months), and confirmation by genetic testing occurred at a mean age of 7.3 months (minimum 4 months, maximum 13 months). The patients were alive

Table 3
Clinical features of the four patients with infantile SMA.

Case No.	Birth year (Sex)	Type	Genotype	Onset age (Initial symptoms)	Age at diagnosis	Highest motor function	Respirator (Tracheotomy)	Present status
1	2012 (Male)	1	*SMN1*: 0 *SMN2*: 2	2 months (Hypotonia)	4 months	No head control	3 months (7 months)	Bedridden
2	2013 (Male)	1	*SMN1*: 0 *SMN2*: 2	1 month (Hypotonia)	4 months	No head control	3 months (5 months)	Bedridden
3	2014 (Male)	1	*SMN1*: 0 *SMN2*: 3	9 months (Unstable sitting)	13 months	Head control at 4 months Supported sitting at 9 months	No (No)	No head control Bedridden
4	2015 (Female)	1	*SMN1*: 0 *SMN2*: 2	6 months (Hypotonia)	8 months	No head control	12 months (12 months)	Bedridden

at the time of the questionnaires, but all were bedridden. Three patients underwent tracheostomy and their breathing was supported by an artificial ventilator.

Case 1 (SMA type 1) was born in 2012. Hypotonia and respiratory insufficiency were noticed at 2 months old. Non-invasive positive pressure ventilation (NIPPV) was started at 3 months. Head control and independent sitting were not observed. The patient underwent tracheostomy at 7 months old. Genetic testing showed that he lacked *SMN1* and carried two copies of *SMN2*.

Case 2 (SMA type 1) was born in 2013. Hypotonia was noticed at 1 month old. Respiratory insufficiency was noticed at 2 months old and NIPPV was started at 3 months. The patient underwent tracheostomy at 5 months old. Head control and independent sitting were not observed. Genetic testing showed that he lacked *SMN1* and carried two copies of *SMN2*.

Case 3 (SMA type 1) was born in 2014. Head control was seen at 4 months old, but he could not sit without support. Motor function gradually deteriorated from 11 months of age, and he eventually lost head control. However, respiratory support was not needed. Genetic testing showed that he lacked *SMN1* and carried three copies of *SMN2*. Although the onset was at 9 months old, he wasn't able to sit up independently. Therefore, we diagnosed the case as SMA type 1. In detail, the case was comparable to type 1c, based on the classifications of Mercuri et al. [21], or type 1b, based on the classification of Kaneko et al. [22].

Case 4 (SMA type 1) was born in 2015. Hypotonia was noticed at 6 months old. Head control and independent sitting were not observed. Tube feeding was started at 9 months old. The patient suffered from aspiration pneumonia at 11 months old. She underwent tracheostomy and respiratory intervention started at 12 months old. Genetic testing showed that she lacked *SMN1* and carried two copies of *SMN2*.

3.2. Epidemiological analysis

Population data were provided by the Statistics Bureau, Ministry of Internal Affairs and Communications of Japan. There were 147,950 births between 2011 and 2015 (Table 2). Thus, the incidence of SMA type 1 was estimated to be 2.7 in 100,000 live births (95% confidence interval, 0.1–5.4).

The population and the number of live births each year in each prefecture are shown in Table 2. Three of the four patients with SMA were born in Ehime Prefecture. The incidence of SMA was estimated at 5.6 per 100,000 live births in Ehime Prefecture (95% confidence interval, −0.7 to 11.9). There was one patient with SMA type 1 in Kochi, and no SMA patients in Kagawa or Tokushima. The incidence of SMA was estimated at 1.1 in these three prefectures (95% confidence interval, −1.0 to 3.1). The incidence in Kagawa, Tokushima and Kochi prefectures is lower than that in Ehime, but the difference was not statistically significant ($P = 0.15$).

4. Discussion

In the present study, the incidence of infantile SMA was 2.7 per 100,000 live births on Shikoku Island. All SMA patients identified in this study were diagnosed with SMA type 1. This is the first report of incidence of infantile SMA based on genetic epidemiology in Japan. Shikoku Island is isolated, and is therefore suitable for such a population-based survey study. Furthermore, the results should be reliable, because the response rate for the questionnaire was 100%, and the diagnoses of all the patients were confirmed by discussions with their doctors and by genetic testing.

Although studies of SMA incidence have been reported before the discovery of *SMN1*, these may be less accurate because the data may contain different diseases with similar symptoms. Recent epidemiologic studies of SMA are based on genetic testing (Table 1). Incidences of all subtypes of SMA were 8.5 per 100,000 live births in Western Sweden [11], 5.0 in Cuba [13], 10.3 in Poland [14], 10.0 in Ohio [15], 6.3–25.5 (median 11.9) in countries in Europe [16] and 5.8 in Taiwan [17] (Table 1).

Using genetic tests, the incidences of SMA type 1 were reported as 3.5, 3.6, 6.9 and 7.1 per 100,000 [11–14], which are similar to the 5.6 per 100,000 live births in Ehime Prefecture. There was a discrepancy in the incidence of SMA type 1 between Ehime and those of the other prefectures of Shikoku Island. Because it is known that diagnostic delay is common in SMA [23], the discrepancy between prefectures may be due to diagnostic delay and/or death of patients prior to diagnosis in the areas with lower incidences. On the other hand, this result suggested that there were more SMA carriers in Ehime than in the other prefectures.

There is no cure for SMA [1]; however, the clinical care of infants and children with SMA has advanced significantly over the past two decades [24]. In addition, the use of new therapeutic drugs can result in incremental achievement of motor milestones and improved motor function scores [25]. In a recent report by Finkel et al. some infants with SMA type 1 under drug therapy developed the ability to sit independently [25]. New therapies are more effective in the early stages of SMA [26].

Considering the severity of the condition, early diagnosis and intervention are required for patients with SMA. For early diagnosis, genetic testing of patients with SMA-like symptoms should be considered. It has been proposed that pre-symptomatic newborn screening should also be considered [24]. In support of its suitability for screening, SMA meets Wilson and Jungner's criteria for disease screening [27,28]. In several countries newborn screening of some babies is already occurring,

while in others screening programs are planned or in development [17,29–31]. In a pilot study of newborn screening for SMA [31], a patient lacking *SMN1* and with two copies of *SMN2* was identified. At 15 days of age, she received her first intrathecal injection of nusinersen. At 12 months old, she had met all of her developmental milestones within the typical temporal profile, and did not require any respiratory or nutritional support. SMA should be considered for addition to the recommended uniform newborn screening panel [31].

Although all the hospitals answered the questionnaire, we might not have detected all SMA patients in this study period, because some SMA-positive patients may have died without ever being diagnosed. And, in our study, we were not able to detect SMA patients who moved out of Shikoku. We realize these are our study's limitations.

In conclusion, the incidence of infantile SMA on Shikoku Island, a regional area of Japan, was estimated to be 2.7 per 100,000 live births. There was a difference in the incidence of SMA between Ehime and the other prefectures of Shikoku Island. This result might suggest that there are some cases of diagnostic delay of SMA, perhaps because of the rarity of the disease. Genetic testing is needed for early diagnosis and treatment of potential SMA patients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.07.016.

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