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**Requested review <Historical note>**


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**“Endemic paraplegia of Koza in Kii” in *Honcho Koji Innen Shu* published in 1689  
is probably the earliest description of amyotrophic lateral sclerosis  
of Kii Peninsula: Presentation of the original and investigation of factuality**

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**Abstract:** High prevalence of amyotrophic lateral sclerosis (ALS) in Kii Province (Kii) located in southern Kii Peninsula was first pointed out by Kinnosuke Miura in 1911, and epidemiological studies by Kiyoshi Kimura et al. verified extremely high incidence after World War II. In 1970s, Yoshiro Yase pointed out that “endemic paraplegia of Koza in Kii” in *Honcho Koji Innen Shu* published in 1689 would mean the same disorder as that of ALS and be the earliest description of Kii ALS although he gave no clear grounds. In this study, the original of the article was presented with an English translation, and factuality of it was investigated from the viewpoints of geography, geology, culture and history of Kii. As a result, it was shown that the article was probably written based on historical events and that the “endemic paraplegia” meant the same disorder as Kii ALS. The author has concluded that “endemic paraplegia of Koza in Kii” is likely to be the earliest description of Kii ALS since ALS is included in the causes of paraplegias of these kinds.

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**Key words:** amyotrophic lateral sclerosis, Kii Peninsula, history, literature, ALS

## Introduction

The extraordinarily high prevalence of amyotrophic lateral sclerosis (ALS) among inhabitants of southern Kii Peninsula corresponding to *old Kii Province* (Kii) in the *Tokugawa period* was first pointed out by Kinnosuke Miura in 1911<sup>1)</sup>. However, the folklore of “*Kii no ashinae byo*” (“*mysterious endemic paraplegia of Kii*”) had been handed down from generation to generation for hundreds of years among native people of Kii. (Yoshiro Yase, personal communication). In the 1960s, Kiyoshi Kimura, Yase and their colleagues investigated the epidemiology of ALS among inhabitants of municipalities of southern Kii Peninsula and discovered extremely high prevalence and incidence foci of ALS in Kozagawa in Wakayama Prefecture and Hohara in Mie Prefecture<sup>2)3)</sup>. The follow-up studies in these two foci showed that the incidence of ALS had been highest during the period of the first systemic studies in the 1960s and continuously declined thereafter<sup>4)5)</sup>, indicating that the incidence

had peaked far before the study was started. To elucidate when the high incidence had occurred, old historical materials including not only written literature and documents but also folklore handed down from generation to generation among native people were examined.

In the early 1970s, Yase examined *Iseido Sosho*<sup>6)</sup> and found a description of “*mysterious endemic paraplegia of Koza in Kii*” in a story entitled “*Kishu Koza no sho fuko no hito*” in a reprint of *Honcho Koji Innen Shu* published in 1689<sup>7)</sup>, one of the reprints of 18 old books compiled into *Iseido Sosho*. (Yase, personal communication). He considered it to be the same disorder of that of endemic Kii ALS at present and introduced it as the earliest description of Kii ALS in the literature although he gave no clear grounds<sup>8)9)</sup>.

The aim of the present paper is to present the original text of *Honcho Koji Innen Shu* written in early modern Japanese<sup>10)</sup> together with its translation into English, and investigate its factuality from the viewpoints of geography, geology, culture and

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history of Kii. Prior to the presentation, the author first introduces geography, geology, history and culture of Kii, and second summarizes the history of early epidemiological studies of Kii ALS because the knowledge of Kii and of history of research is necessary for the readers to understand the article.

### I. Geography, Geology, History and Culture of Kii

Kii Peninsula (Kii Hanto) of Honshu Island is the largest peninsula of Japan (Fig. 1, squared area) and located south to the median tectonic line (fine dashed line)<sup>11</sup>. Geologically it is located on the southern edge of the Eurasian Plate which overrides the Philippine Sea Plate, and the interface between the two plates forms an epicenter named Nankai Trough (Fig. 1, thick dashed line). Nankai Trough caused big earthquakes and tsunamis<sup>12</sup>, and repeated incidences of destructive earthquakes and tsunamis to the coastal area of Kii Peninsula after the 7th century were documented (Table 1)<sup>13</sup>.

Historically, the southern Kii Peninsula had been called *Kumano Province* (Fig. 2, the shadowed area) until the mid-7th century when it was incorporated in *Kii Province* called Kii or Kishu (Fig. 2, the area bordered by thick solid line) and renamed as *Muro County*<sup>14</sup>. In 1879, the Meiji government reorganized

*Muro County* by dividing it into four new counties including Kita (north)-Muro County and Minami (south)-Muro County belonging to Mie Prefecture<sup>15</sup>, and Higashi (east)-Muro County and Nishi (west)-Muro County belonging to Wakayama Prefecture<sup>16</sup> as shown in Fig. 2.

Religiously, *Kumano Province* (*Muro County* of Kii) has been regarded as the Holy Land of Japanese Shintoism since the 7th century when the three sacred Grand Shrines of Japanese Shintoism (*Taisha*) were built<sup>17</sup>. They are called *Kumano Sanzan*; *Kumano Hayatama Taisha Grand Shrine* in Shingū, *Kumano Nachi Taisha Grand Shrine* and neighboring *Nachisan Seiganto-ji Temple* in Nachi-Katsuura, and *Kumano Hongū Taisha Grand Shrine* in Hongū (Fig. 2). Many pilgrims came from Kyoto (the capital of Japan from 794 through 1869) and Osaka via a network of routes “the Kumano Pilgrimage Routes,” now called “the Kumano Kodo” (Fig. 2: middle-sized dashed lines from Kyoto via Osaka or from Ise via Owase, to Hongū, Shingū and Nachi). In July 2004, “the Kumano Kodo pilgrimage routes” were registered as UNESCO World Heritage as part of the “Sacred Sites and Pilgrimage Routes in the Kii Mountain Range” property<sup>18</sup>.

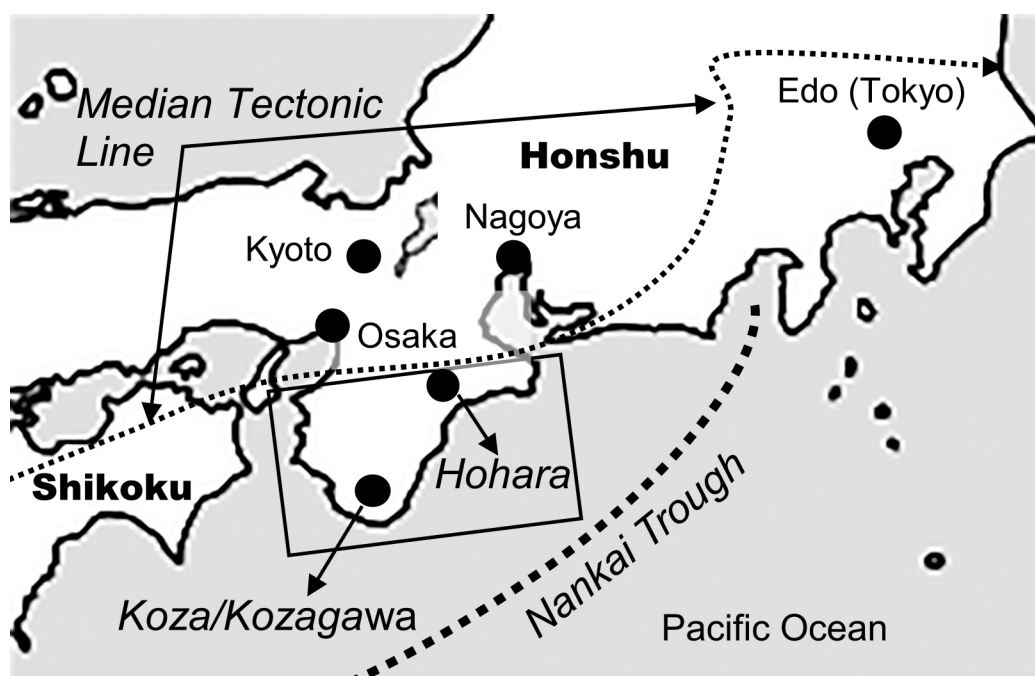


Fig. 1 The central area of Honshu Island of Japan.

Kii Peninsula (the area surrounded by a square) is located in western Honshu Island of Japan and is geographically defined as the outer zone of the south of “Median Tectonic Line” (the fine dotted line) that divides Honshu Island into the north and the south<sup>11</sup>. Seismologically, Kii Peninsula is located on the southern edge of the Eurasian Plate which overrides the Philippine Sea Plate, and the interface between the two plates forms an epicenter named “Nankai Trough” (the bold dashed line) that runs through the Pacific Ocean approximately 100 km apart south to the coast of Kii Peninsula<sup>12</sup>.

**Table 1** Huge earthquakes and tsunamis with the Nankai Trough as the epicenter recorded in the documents (Made by the author from the data of Watanabe<sup>13)</sup>).

西暦	和暦（元号）			
Year/month/day (AD)	Japanese era corresponding to the reign of one emperor		Estimated magnitude (M)// Height of tsunami (meter)	Additional reports in the documents
684/11/29	天武	Tenmu 12/10/14	8.4// 10–20 m	
887/8/26	仁和	Ninna 3/7/30	8.6// 10–20 m	
1408/1/21	応永	Ōei 14/12/14	7.0// 2 m	
1498/9/20	明応	Meiō 7/8/25	8.6// 10–20 m	Temples and shrines in Kumano and Nachi collapsed, 10,000 drowned in Ise-Shima
1520/4/8	永承	Eishō 17/3/7	7.0// 2 m in Kii	Temples and shrines in Kumano, Shingū and Nachi collapsed,
1605/2/3	慶長	Keichō 9/12/16	7.9// 4–5 m in Kii	700 houses washed out by tsunami in west coast of the Kii peninsula
<b>1645–1647</b>	<b>正保</b>	<b>Shoho</b>		<b>The years of the 92nd story of Kinbei Yamamoto in <i>Honcho Koji Innen Shu</i></b>
<b>1689</b>	<b>元禄</b>	<b>Genroku 2/3/ a lucky day</b>		<b>Year of publication of <i>Honcho Koji Innen Shu</i></b>
1707/10/28	宝永	Houei 4/10/4	8.4// more than 30 m	1,000 drowned in Owase 1854/12/24
1854/12/24	嘉永	Kaei 7/11/5	8.4// 9 m in Kushimoto, Kii	40,000 houses destroyed, 3,000 dead
1944/12/7	昭和	Shōwa 19/12/7	7.9// 8–10 m	998 dead, 3,059 injured, more than 75,000 housed destroyed
1946/12/21	昭和	Shōwa 21/12/21	8.0// 4–6 m	1,330 dead, 3,942 injured, 102 missing, more than 42,000 houses destroyed
1948/4/18	昭和	Shōwa 23/4/18	7.0// 0.5 m	

## II. Brief history of research of epidemiological aspects of Kii ALS

In 1911, Miura\* first pointed out the extraordinarily high prevalence of ALS in Owase of Kita-Muro County of Mie Prefecture (Fig. 2) in a lecture on ALS at the School of Medicine of the University of Tokyo<sup>1)</sup>. In 1918, Nishikawa reported that he had examined a considerable number of patients with ALS in Shingū of Higashi-Muro County of Wakayama Prefecture (Fig. 2)<sup>19)</sup>. In 1920, Irizawa, Professor of Internal Medicine, the University of Tokyo reported that at the University Hospital he examined many ALS patients from Kii<sup>20)</sup>. Nagai and his colleagues conducted a survey of patients with ALS in Muro Counties of Mie Prefecture and Wakayama Prefecture in the summer 1923, and reported three patients in Owase and one in Shingū<sup>21)</sup>. Additionally, they heard from indigenous residents that not only the immigrants into Muro Counties from elsewhere but also the emigrants to the other areas from Muro County had suffered from ALS. In 1925, Hirata investigated the native place (prefecture) of 56 patients with ALS who had been admitted to the University of Tokyo Hospital and found that seven of them were from Mie Prefecture, which was the largest number of the 47 prefectures<sup>22)</sup>. Through these studies in early 1900s, the view

that the prevalence of ALS is extraordinarily high in Muro Counties of Mie Prefecture and Wakayama Prefecture became widely accepted and established.

Epidemiological studies on the incidence of ALS in Muro Counties began after World War II. During the 1960s, Kimura, Yase and their colleagues of Wakayama Prefectural Medical University conducted investigation of the prevalence and incidence of ALS in the municipalities located in southern Kii Peninsula and discovered extremely high prevalence and incidence of ALS in Kozagawa of Wakayama Prefecture and Hohara of Mie Prefecture<sup>23)</sup> (small white circles in Fig. 2). The follow-up epidemiological studies revealed that the incidence of ALS was the highest in the 1960s when they had started the study and it gradually declined until the 1980s when occurrence of new patients was reported to have disappeared<sup>4)5)</sup>. These findings indicated that the high incidence of ALS was already in the declining phase when the study was started in the 1960s, suggesting that it had peaked long before the early 1900s when it was first reported<sup>1)19)–22)</sup>. Consequently, the next aim of research turned to clarify when the high incidence of ALS had occurred and been recognized.

Yase took notice of the old folktale of “*Kii no ashinae byo*” (“*mysterious endemic paraplegia of Kii*”) or “*Muro byo*” (“an



Fig. 2 Map of Kii Peninsula showing important places in the present paper.

Kii (*Kii Province*) is shown as the area surrounded by a bold solid line. The territory of *Muro County* is shadowed by fine horizontal lines. Its northern area including *Kita-Muro County* and *Minami-Muro County* belongs to *Mie Prefecture*, and its southern area including *Higashi-Muro County* and *Nishi-Muro County* belongs to *Wakayama Prefecture*, as partitioned by the finely dashed lines. The high incidence foci of ALS, *Kozagawa* of *Wakayama Prefecture* and *Hohara* of *Mie Prefecture* are shown by small white circles. A network of routes “*the Kumano Pilgrimage Routes*,” now called “*the Kumano Kodo*” are shown by middle-sized dashed lines from *Kyoto* via *Osaka* or from *Ise* via *Owase*, to *Hongū*, *Shingū* and *Nachi*.

endemic disease of *Muro County*”) and investigated not only written materials but also orally transmitted folktales handed down from generation to generation among native people. In the early 1970s, he examined *Iseido Sosho*<sup>6)</sup> at the Kanazawa University Library, and found a story describing “*mysterious endemic paraplegia of Koza in Kii*” in a reprint of *Honcho Koji Innen Shu* published in 1689<sup>6)</sup> (Yase, personal communication). *Iseido Sosho* was edited and published by Shuzo Kure\* in 1923. It is a library of reprints of 18 old books on medicine and psychiatry published in Japan before the 19th century and a reprint of *Honcho Koji Innen Shu* is included in it. “*Mysterious endemic paraplegia of Koza in Kii*” is described in the 92nd story

entitled “*Kishu Koza no shou fuko no hito*” as shown later. He considered that it meant the same disorder as that of endemic ALS of the *Kozagawa* focus at present, and pointed out that it would be earliest description of Kii ALS in the literature ever known although he gave no clear grounds or evidence<sup>8)9)</sup>.

\*Note. Kinnosuke Miura (1864–1950) and Shuzo Kure (1865–1932): the co-founders of Japanese Society of Neurology and Psychiatry (1902)

Kinnosuke Miura<sup>23)</sup> graduated from School of Medicine, the University of Tokyo in 1887 and studied internal medicine under Erwin Baelz, one of the invited Professors from Germany. From

1889 to 1892, he stayed in Europe and studied internal medicine and neurology. He studied German neurology under Carl Gerhardt and Hermann Oppenheim in Berlin, Felix Marchand in Marburg and Wilhelm Heinrich Erb at the University of Heidelberg. In January 1892, he moved to Paris and studied French neurology at Jean-Martin Charcot in his later years until November 1892 when he returned to Japan. In 1895, he was appointed as the Chair and Professor of Internal Medicine of the University of Tokyo (1895–1924), and taught internal medicine including neurology until his retirement. He was one of the founders of Japanese Society of Internal Medicine established in 1903. He is respected as the founder of neurology of Japan.

Shuzo Kure<sup>24)</sup> graduated from the University of Tokyo School of Medicine in 1890. He was appointed as an associate professor of psychiatry in 1896. From 1897 to 1901, he stayed in Austria and Germany and studied psychiatry, neurology and neuropathology. He studied them under Heinrich Obersteiner and Richard Freiherr von Krafft-Ebing at the University of Vienna and under Emil Kraepelin, Franz Nissl and Wilhelm Heinrich Erb at the University of Heidelberg. In 1901 when he returned to Japan, he was appointed as the Chair and Professor of Psychiatry (1901–1925) of the University of Tokyo. In 1902, he established the Psychotic Charity Relief Society. In 1923, he edited and published *Iseido Sosho*, a library of old medical books particularly on psychiatry, psychology and neurology. He founded the Japanese Society of Medical History in 1927. He is respected as the founder of Psychiatry of Japan.

### III. “*Honcho Koji Innen Shu*” published in 1689

Yase found the description in a reprint of *Honcho Koji Innen Shu*<sup>7)</sup> collected in *Iseido Sosho*<sup>6)</sup>. (Yase, personal communication). In the present study, the original text of *Honcho Koji Innen Shu* owned by Kyoto University Library<sup>10)</sup> was used with its permission.

#### 1. The book title and cover design

The book title, “*Honcho Koji Innen Shu*” means a collection (“*Shu*”) of mysterious stories, tales and legends in the past (“*Koji*”) which had been handed down in Japan (“*Honcho*”), with explanation by “*Innen*” - the karma in Buddhism that means the fate as effect from cause of the individual mysterious phenomenon and events. It contains 156 short mysterious stories and legends collected in the 17th century from all over Japan. Each story usually consists of two parts: first, a presentation of real-looking but mysterious events, and second, comments of the writer and explanation by the karma (its effect and cause) to be learned from the story.

The book is woodblock-printed with Chinese ink on fine Japanese paper (Fig. 3). It is written in kanji (Chinese character)

and kata-kana (angular Japanese phonetic syllabary) of early modern Japanese. The editor/writer is anonymous. It consists of five volumes, and each volume is bound with a front cover dyed deep blue with indigo plant dye (Fig. 3, A) on which the book title and the volume number are printed. On the back cover (Fig. 3, B) are printed the date of publication in the center - the second year of the *Genroku era* of the *Tokugawa period* (1689 A.D.), the publisher’s name and address on the right - *Seibe Yorozyu* in *Aomono-cho, Edo* (old name of Tokyo before 1868), and the printer’s name and address on the left - *Shobei Kariganeya* in Osaka.

#### 2. Chapter 92. A story entitled “*Kishu Koza no shou fuko no hito*” (Fig. 4)

“*Mysterious endemic paraplegia of Koza in Kii*” is described in the 92nd story entitled “*Kishu Koza no shou fuko no hito*”. It consists of four parts: line 1: a short title, lines 2 and 3: one sentence summarizing the story, lines 4–8: the text telling a story of two unfortunate events that *Kinbei Yamamoto*, an unfilial son from Koza Village (*Koza no shou*) met with, and lines 8–9: the writer’s conclusive comments on the lesson to be learned from the story.

#### 3. The original text written in early modern Japanese (Fig. 4) with its phonetic notation in alphabets and its translation into English

##### Part 1 (line 1).

The first line, “*Kishu Koza no shou fuko no hito*” represents the title of this chapter.

[The unfortunate fate of unfilial inhabitants (*fuko no hito*) of Koza Village (*Koza no shou*) in Kii Province (*Kishu*)]

##### Part 2 (lines 2 and 3).

“*Kishu Koza to iu tokoro nite wa fuko ni fuko no mono ha michi wo ayumu koto kanawazu. tsuini ashinae to nareri*”

[In *Koza of Kii*, those unfilial to their parents would never be forgiven and would be punished by making them paralyzed and unable to walk.]

##### Part 3.1 (from line 4 to line 5).

“*hyo ni iwaku, fuko ni fuko ha ten chi mo irezu to nareba, izure no kuni nite mo kaku no gotoku aritaki mono nari*”

[It has been said that inhabitants lacking filial piety in *Koza of Kii* would be never forgiven. May all the individuals unfilial to his/her parents be punished throughout Japan as those in *Koza*, by making them paralyzed and unable to walk!]

##### Part 3.2 (from line 5 to line 8).

“*Shoho nen chu ni Yamamoto Kinbei to iu mono, chichi to chuzetsu shite Kamigata ni noboru toki, Nachi nite ashi nae, yado*

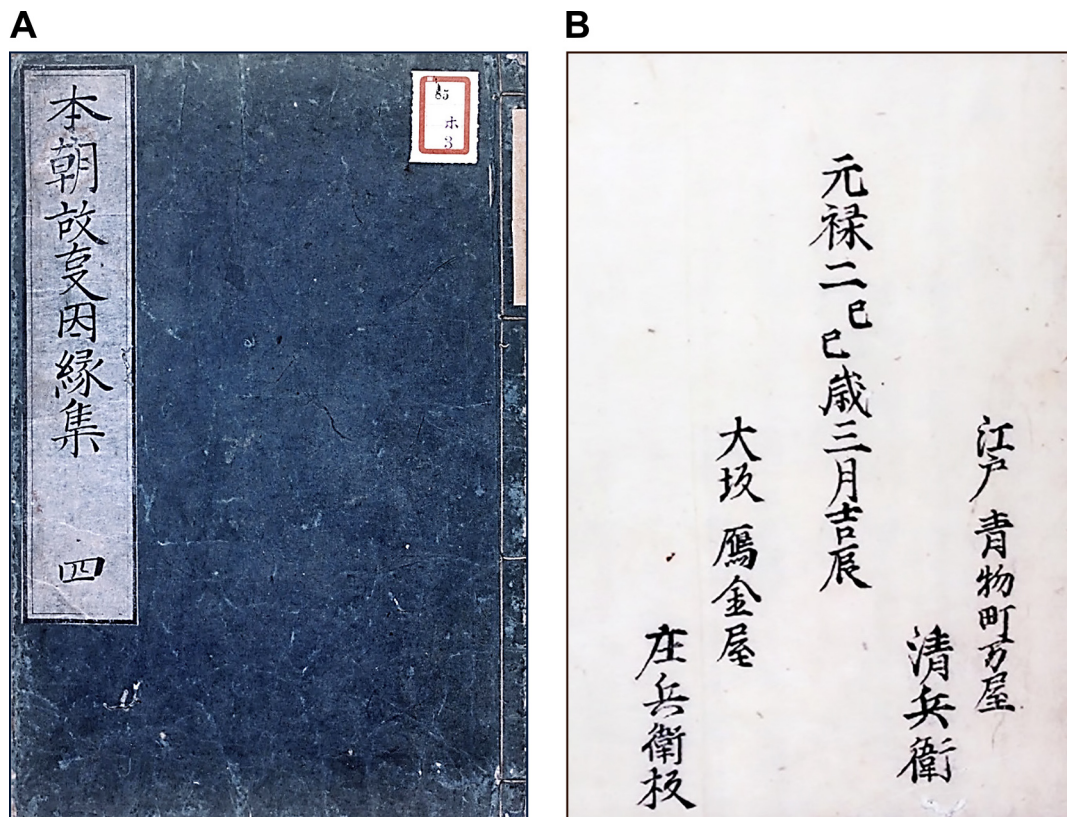


Fig. 3 Pictures of the front cover (A/left) and back cover (B/right) of the original text of *Honcho Koji Innen Shu*<sup>10)</sup>.

(Property of Kyoto University Library). Used with permission.

The front cover (A/left) is dyed deep blue with indigo plant dye on which the title and the volume number are printed. On the back cover (B/right) are printed the date of publication in the center - "The second year of the *Genroku* era of the *Tokugawa* period" (1689 A.D.), the publisher's name and address on the right - "*Seibe Yorozyu* in *Aomono-cho*, *Edo*" (old name of Tokyo before 1868), and the printer's name and address on the left - "*Shobei Kariganeya* in *Osaka*".

*wo karireba sono ie kuzure, hama no do ni fuseba sono do mo taoru. yue ni tsui ni kokyo ni kaeru to nari.*"

[In the *Shoho* era (1645–1647) of the *Tokugawa* period lived a man named *Kinbei Yamamoto* in *Koza Village of Kii*. He lacked filial piety to his parents and did not respect them at all. One day after he had a quarrel with his father, he ran away from home and headed to *Kamigata* (the urban area including Kyoto and Osaka shown in Fig. 2), leaving his parents behind. When he arrived at *Nachi*, he became paraplegic and unable to walk at all, so that he was forced to stay in an inn. Then a catastrophic disaster struck *Nachi* and destroyed all the houses and buildings including the inn and the temple where he had sheltered. He could not but give up to go to *Kamigata* after all and went back to his home in *Koza*.]

Part 4 (from line 8 to line 9)

*"fushigi no sho nari. kore nite fuko no tsumi wo siru beshi"*

This paragraph says the writer's comments. [*Koza* is a mysterious place where inhabitants lacking filial piety would

suffer from mysterious paraplegia and become unable to walk. Native people believe that those lacking filial piety in *Koza* would be punished with paraplegia. This story teaches us the lesson - "Be filial to your parents, or you would be punished for causal retribution!"]

#### IV. Investigation of factuality of the story from the viewpoints of geography, geology, culture and history

*Honcho Koji Innen Shu* consists of 156 short mysterious stories collected in the 17th century. They were edited to preach ordinary uneducated people the lessons to be learned from the stories<sup>25)</sup>. The 92nd story tells the importance of filial piety to parents, one of the most important Confucian morals<sup>26)</sup> by using the two unfortunate events of *Kinbei Yamamoto* as examples of retribution for a lack of filial piety. In these situations, the story must have sounded real and persuasive if it contained actual events that were well known by the listeners. Therefore, the



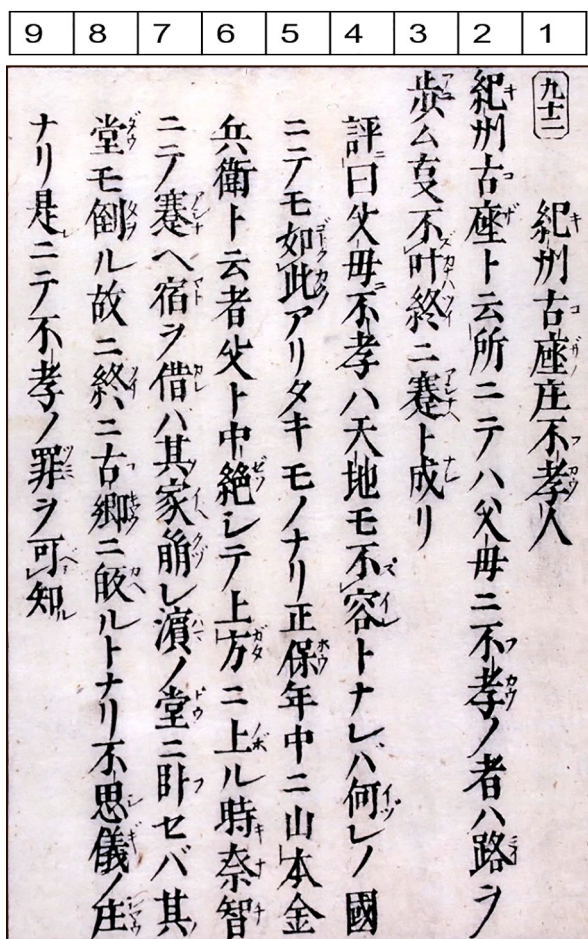


Fig. 4 The photograph of the 92nd story in volume 4 of the original text of *Honcho Koji Innen Shu*, written in early modern Japanese with kanji and kana.

Each line is numbered from the beginning on the right to the end on the left. Refer to the text for the alphabet notation, English translation and meaning.

author investigates factuality of the story to verify whether "mysterious endemic paraplegia of Koza" and "the mysterious catastrophic disaster in Nachi" in the story were mere fictions or really existed.

#### 1. Factuality of existence of Kinbei Yamamoto from Koza Village in Kii

The main character "Kinbei Yamamoto" represents a bad unfilial son who was punished with paraplegia for his lack of respect to his parents. He is portrayed as if he really existed in the story, implying that he was a legendary person well known among people in Kii at that time. In addition, "Koza no shou" in *Honcho Koji Innen Shu* refers to old Koza Village during the Tokugawa period which covered the area along the Koza-river (Koza-gawa) including the area of Koza and Kozagawa at present (Fig. 2).

#### 2. Nature of "paraplegia of Koza"

Kinbei Yamamoto developed motor paraplegia of acute or subacute onset and of chronic course without remission or recovery. There is no description of accompanying symptoms such as fever, pain, abnormal sensations, micturition difficulties and cognitive abnormalities, and there is no description on the diagnosis as well as the course and consequences of his illness. Motor paraplegia can be caused by such neurological abnormalities of various nature in muscles, peripheral nerves, spinal cord and brain as ALS and other motor neuron diseases, various myopathies and muscular dystrophies, motor neuropathies and neuronopathies, myelopathies and spine diseases, and many brain diseases<sup>27)</sup>. Paraplegia of acute or subacute onset can be caused by vitamin-deficient neuropathies, demyelinating neuropathies such as Guillain-Barré syndrome and chronic autoimmune neuropathies, multiple sclerosis and neuromyelitis optica. Lack of abnormalities in sensation and micturition or lack of recovery or remission in the clinical course is exceptional in these paraplegias but common in ALS/motor neuron disease. Therefore, ALS can be included in one of the causal diseases of Kinbei's disorder.

In addition, the pattern of endemic occurrence of "mysterious endemic paraplegia among inhabitants of Koza Village for generations" resembles that of endemic ALS in the Kozagawa focus having occurred for generations. These similarities between the two disorders imply that they may have been caused by the same disease.

#### 3. Factuality of "catastrophic disaster" reminiscent of a big earthquake and tsunami

While he stayed in Nachi, Kinbei Yamamoto encountered "a catastrophic disaster" which destroyed almost all the houses, temples and buildings along the coastal area of Kii Peninsula. Although no specific explanation to account for what the disaster was is described, there is no doubt that it was a big earthquake and tsunami because repeated disastrous earthquakes and tsunamis to Nachi and neighboring coastal area after the 7th century were recorded (Table 1)<sup>13)</sup>. However, no big earthquake or tsunami was recorded during the four years of the Shoho era (1645–1647), and the Great Earthquake and Tsunami of the Keicho era" occurred on February 3, 1605 A.D. (the 16th day of the 12nd month of the 9th year of Keicho)<sup>13)</sup>, more than 40 years before the Shoho era (1645–1647). The time gap can be explained if the two well-known historical events - "the catastrophic disaster in Keicho era (1605)" and "Kinbei's paraplegia during Shoho era (1645–1647)" were superimposed by mistake or intentionally, when the story was compiled in 1689.

#### 4. Conclusion of the investigation to verify factuality of the story

The author investigated the factuality of the story in *Honcho*

*Koji Innen Shu*<sup>10)</sup> from the viewpoints of geography, geology, culture and history of Kii, and appreciated that the two events - “*mysterious endemic paraplegia of Koza Village in Kii*” and “*the catastrophic disaster*” were not mere fictions but written based on the historical events. As a result, the *endemic paraplegia* seemed to have really existed and to mean the same disorder as that of ALS although the grounds were circumstantial. Therefore, the author has concluded that “*mysterious paraplegia of Koza in Kii*” in *Honcho Koji Innen Shu* is likely to be the earliest description of endemic Kii ALS in the Koza-Kozagawa area as Yase pointed out<sup>8)9)</sup>.

## Discussion

Extraordinarily high prevalence of ALS in the isolated Western Pacific islands was discovered in the 20th century independently: among inhabitants in southern Kii Peninsula of Japan by Miura in 1911<sup>1)</sup>, among Chamorros on Guam by American physicians in Official Death Records beginning in 1904<sup>28)</sup> and by Mulder and Kurland in 1954<sup>29)</sup>, and among Auyu and Jakai speaking people living on a wetland plain in southern West New Guinea by Carlton Gajdusek in the late 1950s<sup>30)</sup>. Epidemiological studies on the incidence of ALS in these high prevalence foci conducted after World War II revealed very high incidence rates of more than 50 times of those in the other areas in the world<sup>31)</sup>.

The three hyperendemic foci of ALS of small population were geographically and culturally isolated from the surrounding societies, so that they were considered not to suffer from the confounding factors that existed in more technologically complex societies. Many epoch-making new discoveries to lead better understanding of the causes or fundamental mechanisms of neurodegenerative diseases were expected<sup>31)</sup>, but very few discoveries to break through neurodegenerative disease research were clarified except for the epidemiological findings. As to the reason of poor results, Garruto pointed out that the disease might already have been in decline at the time of the first systematic epidemiological studies in the mid-20th century and that the disease must have broken out decades or hundreds of years before the start of the studies, be it genetic, environmental, or some combination of a gene-environmental interaction<sup>31)</sup>. Consequently, he emphasized that historical events in these foci were important to clarify any impact they might have on the etiology and mechanisms of pathogenesis.

Yase investigated old literature and documents written before the 19th century and found a description of “*mysterious paraplegia of Koza in Kii*” in a story in *Honcho Koji In'nen Shu* published in 1689<sup>7)</sup>. He introduced it as the earliest description of Kii ALS in the literature, but did not give obvious grounds<sup>8)9)</sup>. The author investigated factuality of the story from the

viewpoints of geography, geology, culture and history of Kii and appreciated that “*mysterious paraplegia of Koza*” seemed to have existed and to mean the same disorder of that of Kii ALS of the hyperendemic focus of Kozagawa at present.

On Guam, death certificates were usually written in Spanish during the early years of American Occupation (1898–1920), and there were many in which the cause of death was listed as “*paralytico*” or “*lytico*,” the term that Chamorros use for ALS. So, ALS has been prevalent on Guam at least since 1815<sup>32)</sup>. As to the recognition of ALS before that, Chen took notice to a legend of “*cursed paraplegia of Guamanian Chamorros in Umatac*” that had been circulated among native Chamorros since the 17th century<sup>23)</sup>. The legend says: ‘*A Spanish priest in Umatac cursed the villagers to be paralyzed so that they could not climb up trees to steal mangos.*’ Chen considered it to be the earliest recognition of ALS on Guam because historically Umatac had the highest prevalence rates of ALS and the legend was probably made up in the late 17th century when the islanders had begun to contact with outsiders of Jesuit mission to Micronesia in 1665<sup>28)</sup>.

These findings indicate that existence of ALS seems to have been recognized by native inhabitants in the 17th century both in Kii Peninsula and on Guam, implying that ALS had broken out before the 17th century at the latest. Previous researches to clarify the causes of high incidence and quick disappearance of Western Pacific ALS were concentrated on the events which had occurred in the 19th and 20th centuries, but the present study as well as that of Garruto<sup>31)</sup> has indicated that investigation of older events and materials before the 18th century based on the old literature, documents, legends and folktales seems necessary and important to verify when and how the endemic ALS had arisen and why it began to decline almost simultaneously in these isolated places.

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