The possibility that the genetic system that adapted the body of highlanders to hypoxia may speed up the development of diabetes with old age, as discussed above, can in fact be understood as "the global environment etched onto the human body."

In a society faced with a growing elderly population, it is vital to consider how the elderly view life and death, as well as how they attribute meaning to their lives.

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Epidemiology

Amyotrophic lateral sclerosis and parkinsonism in Papua, Indonesia: 2001–2012 survey results

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Abstract

Objective Only one previous follow-up study of amyotrophic lateral sclerosis (ALS) and parkinsonism in Papua, Indonesia has been carried out since a survey undertaken in 1962–1981 by Gajdusek and colleagues. Therefore, to clarify the clinical epidemiology of ALS and parkinsonism in the southern coastal region of Papua, the clinical characteristics and prevalence of the diseases in this region were examined and assessed.

Methods Cases of ALS and parkinsonism were clinically examined during a 2001–2012 survey in Bade and other villages along the Ia, Edera, Dumut and Obaa rivers in Papua, Indonesia. Possible, probable and definite ALS was diagnosed clinically by certified neurologists based on El Escorial criteria. The criteria for a diagnosis of parkinsonism were the presence of at least two of the four following signs: tremor, rigidity, bradykinesia and postural impairment with a progressive course.

Results During the survey, 46 cases of ALS and/or parkinsonism were diagnosed within a population range of 7000 (2001–2002) to 13 900 (2007–2012). The 46 cases consisted of 17 probable-definite cases of ALS, including three with cognitive impairment (CI), 13 cases of overlapping possible, probable or definite ALS and parkinsonism, including five with CI, and 16 cases of parkinsonism, including one with CI. The crude point prevalence rate of pure ALS was estimated to be at least 73 (95% CI 0 to 156) to 133 (27 to 240)/100 000 people and that of overlapping ALS and parkinsonism at least 53 (0 to 126) to 98 (2 to 193)/100 000 in 2007, or 2010 in some regions.

Conclusions While the prevalence of ALS in Papua has decreased over the past ~30–35 years, it remains higher than the global average. There was a high prevalence of overlapping ALS, parkinsonism and CI, which has also been previously reported in Guam and Kii.

Strengths and limitations of this study

- This study is a unique epidemiological survey of neurodegenerative diseases from 2001 to 2012 in Papua, Indonesia, an area with one of the highest incidences of amyotrophic lateral sclerosis (ALS) in the world.
- This study recognised significant overlap of ALS with parkinsonism and cognitive impairment.
- This study was based only on clinical findings, so it is limited by lack of electromyogram data, DNA analysis, or any autopsy data from this population, without which it is difficult to determine how these patients fit into sporadic ALS or Parkinson's disease and how they compare with ALS/parkinsonism-

- dementia complex on Guam and in the Kii peninsula.

Introduction

Between 1962 and 1980, Gajdusek *et al* reported 97 cases of amyotrophic lateral sclerosis (ALS), 18 cases of parkinsonism, and 18 cases of poliomyeloradiculitis (PMR) in the southern coastal area of Papua (former Irian Jaya, Indonesia), which had a population of 7000. The high incidence of ALS and parkinsonism in Papua was concentrated around the Ia River.[1,2] Along with Guam and Kii in Japan, Papua (Indonesia) was considered to have the highest incidence of ALS in the world.[1–7] However, the high incidence of ALS and parkinsonism-dementia complex (PDC) in Guam and Kii is reported to no longer exist.[8,9] Furthermore, in 1987, Spencer *et al* reported only two cases of ALS and three cases of parkinsonism in the villages along the Ia River. In 1990, no cases of ALS and three cases of parkinsonism were reported along the same river; thus, it was suspected that ALS has declined or even disappeared in Papua.[10] No follow-up surveys of ALS and parkinsonism have been conducted in Papua since 1991.

To clarify the clinical epidemiological characteristics of ALS and parkinsonism in the southern coastal region of Papua, we conducted a survey of neurodegenerative diseases documented between 2001 and 2012.

Methods

The survey sites for 2001 and 2002 were the villages of Kepi (population 800), Emete (800), Ogoto (400), Senggo (2000) and Bade (3000) for a total population of 7000.[11,12] Between 2007 and 2012, the survey sites were the villages along four rivers, namely Bade on the Digul River (population 3800 people), Mur on the Mappi River (1500), the eight villages along the Ia River (4500), and the 12 villages along the Edera and Dumut rivers (4100 people) for a total population of 13 900. The eight villages along the Ia River were Gimikya (800), Geturki (500), Homlikya (700), Kobeta (600), Asset (600), Osso (300), Bosma (500) and Ogorito (500). The 12 villages along the Edera and Dumut rivers were Benggo (200), Kokoya (500), Sahapikya (400), Harapan (400), Yibin (300), Mopio (300), Pies (300), Memes (300), Habeske (300), Muya (300), Getio (200) and Sien (600) (figure 1). At least two of six Japanese-certified neurologists (KO, MF, YH, SK, YK and KM) visited each village with a local neurologist (IM).

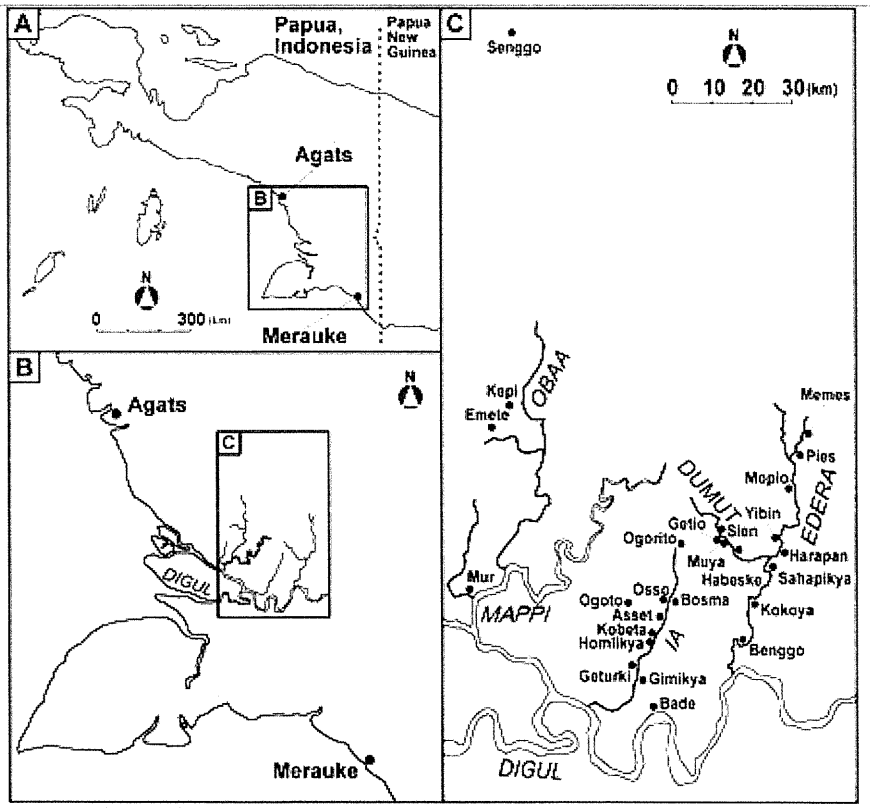

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Figure 1

Map of the field sites. (A) Large-scale map of the southern coastal plain in Papua, Indonesia. (B) Smaller scale map of the southern coastal plain in Papua, Indonesia showing rivers. (C) Detailed map showing villages in the southern coastal area in Papua in which all confirmed cases of amyotrophic lateral sclerosis and/or parkinsonism with/without cognitive impairment were seen from 2001 to 2012.

The village leaders and medical staff from the primary healthcare centre in each village agreed to take part in the survey, which was conducted with the permission of the Department of Health of the Papua Provincial Government in cooperation with Cenderawasih University. The purpose of the neurological examinations was explained to all villagers. All the subjects volunteered to participate after announcement of the availability of neurological check-ups, which were performed in the community health centres or in homes at each field site. While this was not a complete inventory survey, we asked each medical doctor or healthcare worker and the village leader to summon all patients with neurological signs or symptoms, including muscle weakness, gait disturbance, tremor, bradykinesia or cognitive impairment (CI), in each village. All patients who were summoned also volunteered to participate in the study. Indonesian collaborators and those co-authors (an English teacher in Bade Senior High School, Indonesian neurologist IM, and staff from Cenderawasih University) who spoke both English and Indonesian, local people who spoke both Indonesian and the local language in each village, and co-author EG, who spoke English, Indonesian and Japanese, served as translators. Written informed consent was obtained from all study participants. For those participants who could not read/write, verbal communication was carried out with the support of their family members and the translators. All participants agreed to undergo neurological examinations, and

none of the patients declined annual re-examination. The survey was approved by the ethics committees of the Research Institute for Humanity and Nature in Japan and Cenderawasih University in Papua, Indonesia.

Among the many neurological and non-neurological cases encountered, diagnoses of ALS, parkinsonism and CI were based on clinical examinations and discussions among the participating neurologists. ALS was classified as 'definite', 'probable', 'possible' or 'suspected' based on combinations of upper motor neuron (UMN) and lower motor neuron (LMN) signs according to the El Escorial criteria of the World Federation of Neurology.[13] Probable and definite ALS are defined as pure ALS in this report. A diagnosis of parkinsonism required the presence of at least two of the following four signs: tremor, rigidity, bradykinesia and postural impairment with a progressive course without evidence or history of vascular accidents or a history of taking drugs known to induce parkinsonism. The degree of disability of patients with parkinsonism was classified according to the scale of Hoehn and Yahr.[14] Overlapping of possible, probable or definite ALS with parkinsonism was defined as ALS-parkinsonism. CI was diagnosed when loss of memory or impairments of language usage, praxis or executive functions were identified during interview and clinical examination by neurologists. As cognitive functional tests such as the mini-mental state examination were not performed for all of the participants, patients with functional disability complications attributable to CI in activities of daily living or in their livelihood were screened during interview with the patients and their family members. PMR was evaluated using the definition of Gajdusek *et al*[1],[2] that PMR is a subacute paralytic condition reminiscent of Landry–Guillain–Barré syndrome, which combines radicular, or perhaps neuritic, elements with more acute onset and sometimes asymmetric paralysis. Neurological cases with overlapping cerebellar signs (two cases) were excluded from this study.

In Bade and the villages along the Ia, Edera and Dumut rivers, new cases were identified and previously diagnosed cases were followed up and assessed neurologically and documented in 2007, 2008, 2010, 2011 and 2012. Years of death were confirmed, and the durations between the subjective onset of illness and the last survey or death were recorded as durations of subjective illness.

The size of the populations of Bade and the villages along the Ia, Edera and Dumut rivers were determined from a report by the public office of Edera district in 2006.[15] We were informed by the village leaders of the populations of other villages in the survey for the period 2001–2002.

Results

Clinical types of ALS and/or parkinsonism

We identified 46 cases with signs of ALS and/or parkinsonism, including 17 cases with pure ALS (table 1), 13 with ALS-parkinsonism (table 2) and 16 with parkinsonism (table 3). We found no case of pure or dominant dementia and PMR consistent with the definition by Gajdusek *et al*; similarly, no cases of PMR were found by Spencer *et al* in 1987 or 1990.[10] Relevant information about the cases, including neurological signs, age at last survey, age and year of onset, disease duration, certified death year and ethnicity, is shown in tables 1⇓–3. The male-to-female sex distribution was 10 : 7 (male 59%) for ALS, 11 : 2 (85%) for ALS-parkinsonism and 8 : 8 (50%) for parkinsonism. The mean age at last survey was 51.3 years for ALS, 52.9 years for ALS-parkinsonism and 51.6 years for parkinsonism. The mean age at onset was 46.2 years (range 11–68 years) for pure ALS, 49.5 years (11–70 years) for ALS-parkinsonism and 45.8 years (27–64 years) for parkinsonism. The mean duration of subjective illness was 7.0 years (2–20 years) for pure ALS, 6.3 years (2–17 years) for ALS-parkinsonism and 6.3 years (2–14 years) for parkinsonism. We observed overlapping CI in three (18%) of the 17 cases of pure ALS, five (38%) of the 13 cases of ALS-parkinsonism, and one (6%) of the 16 cases of parkinsonism.

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Table 1

Relevant characteristics and neurological signs in cases with pure ALS (n=17) with/without cognitive impairment in Papua, 2001–2012

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Table 2

Relevant characteristics and neurological signs in cases with overlapping ALS and parkinsonism (n=13) with/without cognitive impairment in Papua, 2001–2012

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Table 3

Relevant characteristics and neurological signs in cases with parkinsonism with/without cognitive impairment (n=16) in Papua, 2001–2012

During the follow-up surveys of the cases in Bade and along the Ia and Edera rivers, we observed the following changes in diagnosis: one case from possible ALS to probable ALS (case ALS 10); two cases from parkinsonism to ALS-parkinsonism (cases ALS-P 2 and ALS-P 3), and one case from probable ALS to definite ALS (case ALS 16) complicated with CI. We also identified an instance of a shared family history of parkinsonism (P 6) and ALS-parkinsonism (ALS-P 1). There were family histories of neurological disorders in seven of 17 cases (41%) of pure ALS, two (15%) of 13 cases of ALS-parkinsonism, and six (38%) of 16 cases of parkinsonism (tables 1⇓–3).

Cases of ALS and parkinsonism in Bade and the villages along the Ia, Edera and Dumut rivers between 2007 and 2012

Between 2007 and 2012, we identified four cases of pure ALS, two cases of ALS-parkinsonism, and one case of parkinsonism in Bade (population 3800). In addition, we found seven cases of pure ALS, four cases of ALS-parkinsonism, and three cases of parkinsonism in the villages (population 4500 people) along the Ia river. Between 2008 and 2012, we identified three cases of pure ALS, five cases of ALS-parkinsonism, and six cases of parkinsonism in the villages (population 4100 people) along the Edera and Dumut rivers (table 4).

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Table 4

Cases of amyotrophic lateral sclerosis (ALS) and parkinsonism in the field sites

In the 2007 survey, there were four active cases of pure ALS (crude point prevalence rate 105 (95% CI 2 to 208)/100 000 people), two cases of ALS-parkinsonism (53 (0 to 126)/100 000 people) and one case of parkinsonism (26 (0 to 78)/100 000 people) in Bade. In 2010, there were six active cases of pure ALS (133 (27 to 240)/100 000 people), four cases of ALS-parkinsonism (89 (2 to 176)/100 000 people) and three cases of parkinsonism (67 (0 to 142)/100 000 people) in the villages along the Ia River. In 2010, there were three active cases of pure ALS (73 (0 to 156)/100 000 people), four cases of ALS-parkinsonism (98 (2 to 193)/100 000 people) and five cases of parkinsonism (122 (15 to 229)/100 000 people) in the villages along the Edera and Dumut rivers (table 4).

In the survey during the period 2007–2012, the number of each clinical type (ALS, ALS-parkinsonism and parkinsonism, respectively) was determined for Bade (4, 4 and 1), the villages along the Ia River, namely Ogorito (1, 2 and 0), Bosma (1, 1 and 0), Homlikya (1, 1 and 1), Gimikya (1, 1 and 0), Geturki (1, 0 and 0), Asset (1, 0 and 1) and Osso (1, 0 and 1), and the villages along the Edera and Dumut rivers, namely Yibin (1, 1 and 0), Sien (0, 1 and 2), Pies (1, 0 and 1), Benggo (0, 1 and 0), Harapan (0, 0 and 1), Mopio (0, 0 and 1), Memes (0, 0 and 1), Muya (1, 0 and 0) and Getio (0, 1 and 0).

Case reports

Case ALS 12

A 64-year-old (in 2012) man of the Auyu tribe, a resident of Bosma along the Ia River, in 2010 had a 9-year history of progressive gait disturbance and motor weakness. These symptoms were found to have progressed based on the findings from follow-up check-ups between 2011 and 2012. Neurological examination revealed UMN and LMN signs, including a positive Babinski sign, hyperreflexia with ankle clonus, muscle atrophy, weakness in the tongue and upper and lower limbs bilaterally, and fasciculation in the upper limbs and tongue. He had no CI or sensory disturbance. We diagnosed him as having definite ALS (figure 2A–D). The subject had ALS, and his brother reported that their father had showed tremor and gait disturbance, which were interpreted to be consistent with parkinsonism.

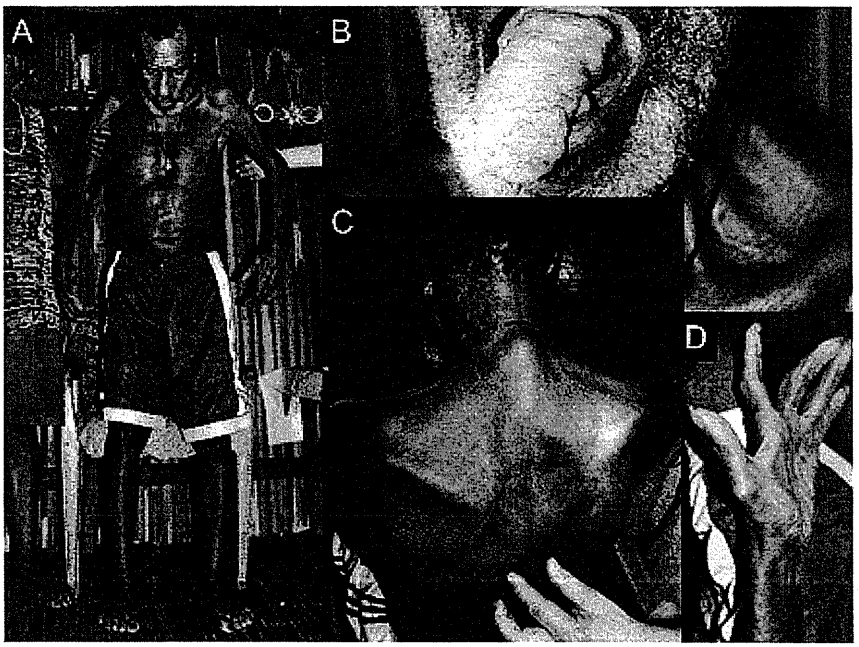

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Figure 2

Patient with amyotrophic lateral sclerosis (ALS) (case ALS 12). (A) The patient needs assistance from family members to stand. (B) Advanced atrophy of the tongue. (C) There is upper limb girdle and truncal muscle atrophy with a positive Babinski sign. (D) Advanced thenar muscle atrophy.

Case ALS-CI 17

A 70-year-old (in 2012) man of the Auyu tribe, a resident of Ogorito along the Ia River, had a history of progressive memory loss for 4 years and slow gait for 2 years. Neurological examination revealed UMN and LMN signs, including a positive Babinski sign, hyperreflexia in the jaw jerk and the bilateral upper and lower limbs, and muscle weakness with atrophy and fasciculation in the distal upper and lower limbs bilaterally. He had fasciculation in the tongue and respiratory muscle weakness with a low oxygen saturation level (SpO_2 86%). He also had memory disturbances accompanied by positive snout and palmomental reflexes and difficulty with mental activities of daily living. He had no sensory disturbance. We diagnosed him as having definite ALS with CI (figure 3A).

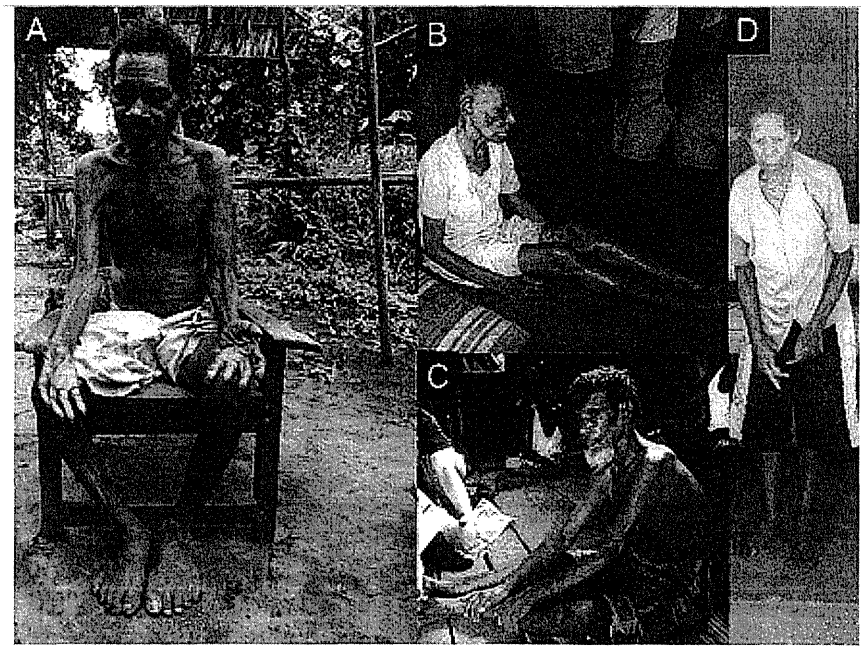

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Figure 3

Patients with amyotrophic lateral sclerosis (ALS), ALS-parkinsonism and parkinsonism. (A) Patient with ALS (case ALS-17) showing muscle atrophy in the distal upper and lower limbs. (B) Patient with ALS-parkinsonism (case ALS-P 1) showing muscle atrophy in distal upper limbs. (C) Patient with ALS-parkinsonism (case ALS-P 7) showing muscle atrophy in the proximal upper limb, shoulder and tibialis anterior. (D) Patient with parkinsonism (case P 7) showing typical parkinsonian hands and anterior bending posture. Parkinsonian hand: striatal deformities of the hand with abnormal postures that are common in patients with advanced Parkinson's disease.

Case ALS-P 1

A 65-year-old (in 2008) woman of the Auyu tribe, a resident of Pies along the Edera River, had a 5-year history of progressive motor weakness and gait disturbance. She could not walk without support. Neurological examination revealed a resting tremor, cogwheel rigidity in the upper and lower limbs, bradykinesia throughout, postural impairment, UMN and LMN signs with a positive Babinski sign, hyperreflexia in the upper and lower limbs bilaterally, and thenar and hypothenar muscle atrophies. She had no CI or sensory disturbance. We diagnosed her as having ALS-parkinsonism and, more specifically, severe parkinsonism (Hoehn and Yahr IV) simultaneously complicated by motor neuron signs indicative of possible ALS. She died in 2009. Her younger sister was case P 6. The subject had ALS-parkinsonism, and her sister reported that their cousin showed tremor and gait disturbance, which were interpreted to be consistent with parkinsonism (figure 3B).

Case ALS-P 2

A 76-year-old (in 2011) man of the Auyu tribe, a resident of Ogorito, had a 5-year history of tremor in both hands in 2010. Neurological examination revealed cogwheel rigidity in his upper and lower limbs, bradykinesia, and UMN signs with hyperreflexia in bilateral upper and lower limbs. We diagnosed him as having parkinsonism (Hoehn and Yahr II) in 2010. He was examined again in 2011, by which time his parkinsonism was complicated by postural impairment, muscle weakness and atrophy, and spasticity of the upper and lower limbs with Babinski signs. He had no CI or sensory disturbance. We diagnosed him as having parkinsonism (Hoehn and Yahr III) with possible ALS; parkinsonism was accompanied by ALS later. He died in 2011 of unknown causes.

We also diagnosed another case of parkinsonism (Hoehn and Yahr III) with possible ALS (ALS-P 3); parkinsonism was accompanied by ALS later.

Case ALS-P-CI 6

A 50-year-old (in 2012) man of the Auyu tribe, a resident of Benggo along the Edera River, had a 2-year history of dysarthria. Neurological examination revealed UMN and LMN signs with a positive Babinski sign, muscle atrophy, and weakness in the tongue, proximal upper limb, shoulder and tibialis anterior muscles. He had cogwheel rigidity in the wrist and elbow, bradykinesia throughout, a positive Myerson sign, and impairment of coordination and postural reflexes. He had memory loss, bradyphrenia, slow speech, and positive snout and palmomental reflexes with difficulty performing activities of daily living. We diagnosed him as having definite ALS and parkinsonism (Hoehn and Yahr III) with CI (figure 3C).

Case P 7

A 52-year-old (in 2010) woman of the Auyu tribe who lived in Mopio along the Edera River had a history of progressive gait disturbance with parkinsonian signs, including resting tremor, cogwheel rigidity, anterior bending, and bradykinesia for 3 years in 2008. In 2008, we diagnosed her as having parkinsonism (Hoehn and Yahr II). By the time of the follow-up survey in 2010, she could not stand by herself and had postural impairment with parkinsonian hands bilaterally. She had no UMN or LMN signs, no CI and no sensory disturbance. We diagnosed her as having parkinsonism (Hoehn and Yahr IV; figure 3D).

Discussion

Internal migration and migration from outside the province are the most significant causes of demographic, social and cultural change in Papua. The populations in the survey sites were composed of former hunter-gatherers who had lived in the forest but had been brought out of the forest and assembled in villages by Dutch colonialists. The villages along the Ia River were founded between 1937 and 1951.[10] An emigration programme called transmigration ('transmigrasi') started in Irian Jaya in 1964 and led to an increase in the number of local migrants and transmigrants from outside Irian Jaya, resulting in various changes, including in the use of food and medicine.[16],[17] As Gadjusek *et al* found a high prevalence of ALS in the first survey in 1962, the neurodegenerative disease must have existed before the introduction of manufactured items.[1]

In the present survey, we performed full neurological examinations in 46 subjects with ALS and/or parkinsonism between 2001 and 2012. Among the subjects, 17 were probable-definite cases of pure ALS, 13 were overlapping ALS (possible, probable or definite) and parkinsonism, and 16 were parkinsonism. Nine cases of ALS and/or parkinsonism had the complication of CI. During the study period, the diagnosis in some patients changed from pure parkinsonism to ALS-parkinsonism, and their disease progressed in severity. Some subjects had both ALS and parkinsonism on their first examination. It is thus evident that overlapping ALS and parkinsonism with or without CI still exists in this region of Papua.

Gajdusek *et al*[1] reported diagnosing 97 cases (57 cases clinically confirmed and 40 cases not clinically confirmed) of ALS during the six surveys they conducted from 1974 to 1981. However, they reported the neurological findings of only 32 of these cases, in only 16 of whom the reported findings of UMN, LMN and parkinsonian signs justify a diagnosis of probable or definite ALS. The 16 cases comprise 12 cases of pure ALS and four cases of overlapping ALS-parkinsonism. Among the 32 ALS patients, three had a positive family history (9%): two had sisters with ALS, and one with ALS-parkinsonism had a family history of ALS. None of the ALS patients had a family history of parkinsonism. The authors also reported their neurological findings in 13 subjects in whom parkinsonism was diagnosed. They reported their findings from full neurological examinations for 10 of these parkinsonism cases. According to their reported neurological signs, these comprised eight patients with parkinsonism, including five with dementia, and two with overlapping ALS-parkinsonism with dementia.[1] Among the 13 patients with parkinsonism, three had a positive family history (23%). In summary, we believe that in the 26 cases reported by Gajdusek *et al*,[1] the full neurological examination findings comprised 12 pure ALS cases (probable or definite), six overlapping ALS-parkinsonism, and eight parkinsonism with/without dementia. Spencer *et al* reported two cases of ALS and three cases of parkinsonism, including one with dementia, in their survey in 1987.[10] They also reported three subjects with parkinsonism overlapping UMN signs, including one with dementia in 1990.[10] We have here reported 17 cases of pure ALS (probable or definite), 13 cases of overlapping ALS-parkinsonism, and 16 cases of parkinsonism with or without CI in the 46 cases we examined fully neurologically. Thus, we identified many cases of overlapping ALS and parkinsonism (n=13, 28%) similarly to previous reports (n=6, 23% and n=3, 38%).[1,10] We also identified many cases with CI (n=9, 20%), also similarly to previous reports (n=7, 27% and n=2, 25%).[1,10] Functional disabilities attributable to CI were recognised in activities of daily living or in their livelihood in all cases with CI in this report.

Gajdusek *et al*[1] reported 13 cases of ALS and three cases of parkinsonism in 1975 in the villages along the Ia River (population 2000). The 13 ALS cases consisted of 10 clinically confirmed cases and three others which were not clinically confirmed. We compared the prevalence of probable-definite ALS and parkinsonism reported by Gajdusek *et al* with our more recent findings. The crude point prevalence of ALS consistent with clinically probable to definite ALS (El Escorial criteria) was between 500 (95% CI 191 to 809)/100 000 people and 650 (298 to 1002)/100 000 people, while that of parkinsonism was 150 (0 to 320)/100 000 people in 1975 along the Ia River. In our 2010 survey (population 4500), we identified six probable-definite cases of ALS in this region (patients ALS 8, 10–13 and 17; 133 (27 to 240)/100 000 people) and seven of parkinsonism (possible ALS-P 2, 3, 9 and 13, and P 10, 15 and 16; 156 (40 to 271)/100 000 people).

Gajdusek *et al* reported eight cases of ALS and six cases of parkinsonism in 1975 in the villages along the Edera and Dumut rivers (population 1950). The eight cases of ALS consisted of seven clinically confirmed cases and one unconfirmed case. The crude point prevalence of ALS consistent with clinically probable to definite ALS (El Escorial criteria) was between 359 (94 to 624)/100 000 people and 410 (127 to 694)/100 000 people, while that of parkinsonism was 308 (62 to 554)/100 000 people in 1975 along the Edera and Dumut rivers. In our survey of this region in 2010 (population 4100), we identified five probable-definite cases of ALS (ALS 9, 14 and 16, and ALS-P 5 and 6; 122 (15 to 229)/100 000 people) and seven cases of parkinsonism (possible ALS-P 10 and 11, and P 7, 8 and 11–13; 171 (44 to 297)/100 000 people; table 4). As this was not a complete inventory survey, the actual prevalence may be a little higher than our estimation.

The population of Bade increased nearly fourfold over 31 years (from 1000 in 1975 to 3800 in 2006), and those of villages along the Ia River (from 2000 to 4500) and the Edera and Dumut rivers (from 1950 to 4100) have increased twofold.[1,15] Only two of the 46 subjects with ALS and/or parkinsonism with/without CI in this survey were born outside Papua (in Maluku). The prevalence of the diseases among the local Papuan residents in this survey may be underestimated compared with the former report after taking into account the increase in the numbers of local migrants from inside Papua and transmigrants from outside Papua.[16–18]

As the median age and life expectancy at the field sites in Papua are estimated to be lower than the global median and fewer people may live beyond the age of 40 or 50 years,[18,19] the prevalence of the diseases in this survey may be underestimated compared with the global mean. As the median age and life expectancy in 1975 may be lower than in 2010,[20] the prevalence of the diseases in the report by Gajdusek *et al* might be underestimated compared with that in our survey.

The prevalence of ALS in this report was found to be three times lower than that found by Gajdusek *et al*. Even after taking into account the changes in population and age structure at the field sites, our findings show that the prevalence of ALS appears to have decreased over the past ~30–35 years since the report by Gajdusek *et al*.[1] This is consistent with the previous report by Spencer *et al*.[10] However, the prevalence is still much higher than the global mean (incidence ~2/100 000; prevalence ~6/100 000)[21–26]; in particular, the prevalence of overlapping ALS and parkinsonism is especially high in Papua.

In the report by Gajdusek *et al*,[1,2] who provided village-by-village data showing the number of cases of ALS and parkinsonism, there were many cases in the remote villages such as Bosma, Pies, Homlikya, Yibin, Sien and Ogorite, which were less visited and least developed. In this survey, many cases (three ALS/ALS-parkinsonism) were found in the remotest village of Ogorito along the Ia River. Two cases of ALS/ALS-parkinsonism were also found in Bosma, Homlikya and Yibin, one ALS and two cases of parkinsonism in Sien, and one case ALS and one of parkinsonism in Pies, which were all remote villages. While there were eight cases of ALS/ALS-parkinsonism in Bade and two in nearby Gimikya, none was reported by Gajdusek *et al* in those sites. This increase may have been brought about by local migrants from affected villages.

Overlapping ALS-parkinsonism and dementia has also been reported in patients with ALS/PDC in Guam and Kii, Japan.[4,27–33] Hirano *et al* provided clinicopathological evidence of 47 cases of PDC in Guam in 1961, comprising the following three groups: 30 cases of PDC; eight cases of parkinsonism with dementia with clinical evidence of UMN impairment; and nine cases of parkinsonism with dementia with clinical evidence of UMN and LMN impairment. At least 15 of these cases (31.9%) had a family history of ALS, parkinsonism or both.[4] Kuzuhara and Kokubo *et al* surveyed neurological diseases in Kii, Japan in the 1990s and found a continuously high incidence of ALS and neuropathologically verified cases of PDC. ALS and PDC frequently affected the same individuals simultaneously and members of the same family. These authors reported 37 cases of ALS/PDC between 1996 and 2006, a high proportion of whom (78%) had a positive family history, as well as clinical examples of pure ALS, PDC and overlapping ALS and PDC. They also reported neuropathological changes common to cases of ALS and PDC in 12 cases of ALS/PDC, resembling those found in patients with ALS/PDC in Guam.[28–33] In our more recent study in Papua, as the previous studies in Kii, Japan and Guam, we identified many cases of pure ALS and ALS overlapping with parkinsonism with/without CI. The prevalence of CI was lower in our study sites than in Guam and Kii.[4,27–33] CI might have been underestimated, and mild CI or mild dementia might have been overlooked by our neurological examinations in the field.

Our study was based only on clinical findings, and limitations include lack of electromyogram data, DNA analysis data, or any autopsy data from this population. Without such data, it is difficult to determine how these patients fit into sporadic ALS or Parkinson disease and how they compare with ALS/PDC on Guam and in the Kii peninsula. However, we did identify many patients with overlapping ALS-parkinsonism in this study. The overlapping of ALS and/or parkinsonism with CI suggests that it may be the same disease entity as the ALS/PDC diagnosed in Guam and Kii.

In Bade, the villages along the Ia River, and the villages along the Edera and Dumut rivers, 53%, 51% and 50%, respectively, of the population were male. There was a high proportion of males especially among subjects with ALS-parkinsonism (85%) and ALS (59%) compared with pure parkinsonism (50%) in our report. The proportion of males was higher among the subjects with ALS (63%) and parkinsonism (76%) in the report by Gadjusek *et al*, in which three of the four ALS-parkinsonism cases were male (75%). The high risks for ALS and PDC among male subjects were recognised in Guam and Kii.[1,7,27]

Indigenous people of Papua still retain aspects of their traditional lifestyles, such as hunting, gathering, fishing and eating sago (from the trunk of *Metroxylon* sp.). They also drink water from shallow wells. However, with the spread of a market economy, recent increases in the numbers of rubber plantations and progress in transportation have been causing lifestyle changes in the villages in the southern coastal area of Papua. Since the diseases are declining as in Guam and Kii, the disease aetiology in Papua may be dominated by environmental factors. Genetic, culture-related and/or family-specific factors may also play a role as evidenced by the family history of disease in 40% of the subjects in this survey in Papua and in 80% in Kii.

Various possible causal genetic and environmental factors for these conditions have been reported. The environmental factors of low concentrations of calcium and magnesium in drinking water were hypothesised.[1,34] There is a recent report showing an association between an increase in ALS incidence and a change in sources of drinking water in the Kii Peninsula.[35] Spencer *et al*[10] pointed out that this explanation was inconsistent with a declining prevalence of ALS in a sessile population dependent on an unchanging supply of river water, which this report may support.

Spencer *et al*[36] reported that cycad seed was used as a poultice in Papua as in Guam. In addition, epidemiological evidence showed that exposure to cycad-derived products was a risk factor for dementia, mild CI and PDC in Guam.[37] Although cycad had been suspected to be the causal factor of ALS in Kii,[38] people in Japan, including the Kii Peninsula, never ate cycad as a daily food, although a small amount of cycad flour in herbal medicine may have been consumed by a few people.[39] We did not examine the association between prior skin wounds and exposure to cycad poultice with the diseases. Skin change and pigmentary retinopathy were not examined in this survey.[40,41] Further studies are needed.

Genetic abnormalities previously established to be associated with familial or sporadic ALS, dementia, familial Parkinson disease and parkinsonism, were sought in the cases in Kii, but none were identified.[28,42] Hermosura *et al*[43] discovered a nuclear mutation in the calcium/magnesium membrane ion channel transient receptor potential melastatin 7 (*TRPM7*) gene in a subset of patients with ALS/PDC in Guam. They reported that a TRPM7 variant that is associated with altered sensitivity to magnesium may have contributed to the pathogenesis of ALS and PDC in two Guamanians. *TRPM7* was not found to be associated with ALS/PDC in the Kii peninsula of Japan.[44] Ishiura *et al*[45] recently discovered a *C9ORF72* repeat expansion in some cases of ALS in the Kii peninsula of Japan; this repeat expansion partly accounts for the high prevalence of ALS in this region. However, the responsible gene(s) remain unproven in almost all cases of ALS/PDC in both Guam and Kii.

Various environmental factors and multiple genetic factors are suggested to be underlying causes of these diseases, but these links are so far unproven.[33,46]

In Guam, although the incidence of pure ALS has declined markedly, the prevalence of PDC is still high.[47] The prevalence of dementia among elderly Chamorros (the earliest known inhabitants of the Mariana Islands, which include Guam) is also reported to be relatively high.[48] In addition, in Kii the incidence of pure ALS has declined markedly, although the prevalence of PDC and ALS/PDC or ALS with dementia has recently increased.[30,33] These changing patterns of ALS/PDC incidence in Guam and Kii might be caused by changes in environmental and socioeconomic factors as well as aging.[48,49]

The mean age of onset in our cases was 46 years for ALS, 53 years for ALS-parkinsonism, and 46 years for parkinsonism. Thus, these subjects were older than the previously reported cases of ALS (33 years) and parkinsonism (43 years).[1] In our cases, the mean duration of subjective illness was 7.0 years for ALS, 6.3 years for ALS-parkinsonism, and 6.3 years for parkinsonism. The duration of ALS in our data was longer than the world mean of 3 years[21–26] and the previously reported 3.5 years for ALS in Papua.[1] The mean age of onset may have recently increased, and the mean disease duration lengthened in subjects with ALS. The prevalence rate of cases with bulbar sign was 37% in 30 cases of pure ALS or ALS-parkinsonian in our report, similar to the rate reported by Gadjdusek (40%) and of classical ALS (39%).[2] The change in onset and course of ALS in recent years might be due to the aging population and changing environmental and socioeconomic factors.

On-going follow-up surveys should be performed to evaluate changes in the clinical types of ALS and/or parkinsonism with or without CI and accompanying changes in environmental and socioeconomic factors, as have occurred in Guam and Kii.

In conclusion, the prevalence of ALS in high-incidence areas in Papuan has decreased over the past ~30–35 years but, in 2010, was still higher than the global average. During this period, there has been an influx of migrants from inside Papua and transmigrants from outside Papua that has increased the size and changed the composition of the population in the villages studied. This expanded population may have had an impact on prevalence estimates. There are still many cases of pure ALS and overlapping ALS-parkinsonism and CI in Papua, as has previously been reported in Guam and Kii. The disease continues to affect native Papuans, but may also affect a small number of non-Papuan immigrants (two of 46 or 3–4%) who adopt the local lifestyle. Environmental factors may play important aetiological roles. Further on-going follow-up surveys focusing on the clinical epidemiology and aetiology of these neurodegenerative diseases in association with ecological and environmental factors in Papua are needed. Future studies, including neuropathological examinations, should be performed when the local villagers in this region of Papua, Indonesia, are willing to consent to autopsies.

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Footnotes

Contributors KO had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KO and KM: study concept and design, and study supervision; KO, TW, MF, MI, EGdSH, SK, YK, HS, RS, IM and KM: acquisition of data; KO, TW, RS, MF and KM: analysis and interpretation of data and drafting of the manuscript; KO: statistical analysis; KO, TW, SK, YK and KM: obtaining funding; KO, PW, ALR and KM: administrative, technical or material support; all authors: critical revision of the manuscript for important intellectual content.

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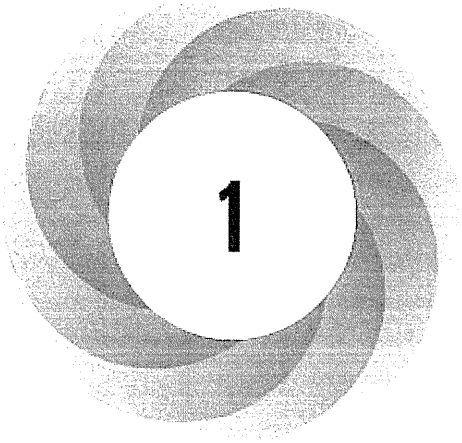

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PREFERRED FEEDING METHODS FOR DYSPHAGIA DUE TO END-STAGE DEMENTIA IN COMMUNITY-DWELLING ELDERLY PEOPLE IN JAPAN

To the Editor: According to a recent systematic review, the prevalence of individuals with dementia among the elderly Japanese population ranges from 2.9% to 12.5% and has been rising gradually over the past few years.[1] One study reported an increase from 5.8% for those aged 65 to 69 to 77.7% in those aged 95 to 99 in 3,394 participants, with Alzheimer's disease being the most frequent cause (67.4%), followed by vascular dementia (18.9%), dementia with Lewy body disease (4.6%), and mixed dementia (4.2%).[2] End-stage dementia, such as Alzheimer's disease, is one of the leading causes of dysphagia. Percutaneous endoscopic gastrostomy (PEG), a method rarely used in elderly adults with degenerative dementia in Western countries, is common in Japan and is used regardless of individual preference. The purpose of this study was to clarify the preference for feeding methods of elderly adults if they develop swallowing difficulty due to end-stage Alzheimer's disease.

Tosa town in Kochi Prefecture had a population of 4,311 in 2012, of whom 1,739 (40.3%) were aged 65 and older. A comprehensive geriatric assessment questionnaire was mailed to 1,615 elderly people (excluding 124 long-term institutionalized individuals) in 2012 with the support of Tosa health staff. The response rate was 60.8% (n = 982) with 587 participants (233 men, 354 women; mean age 76.7 ± 7.6) returning complete questionnaires and 395 with incomplete questionnaires being excluded. Illustrations of feeding methods, including PEG, nasal tube feeding, drip infusion through peripheral vein (DIV), and intravenous hyperalimentation (IVH) were shown to participants along with brief explanations (Figure 1), and participants were asked whether they had experienced any of these methods and whether they had seen these methods administered to their relatives or friends. With regard to participants' own experiences, DIV was the most frequently experienced method (48.4%), followed by IVH (2.2%) and nasal tube feeding (2.0%); none of the participants had experienced PEG. Participants had seen DIV (64.4%), PEG (19.3%), IVH (17.2%), and nasal tube feeding (34.2%) administered to their families or friends.

With an option to choose oral intake only, participants were then asked, "If you cannot take meals orally because of end-stage Alzheimer's disease, which feeding method do you prefer?" As for the preferred method, 42.5% of the participants chose DIV, whereas other artificial feeding methods were chosen much less frequently (IVH, 5.1%; PEG, 4.7%; nasal feeding tube, 4.3%); 50.3% chose none of the four methods, responding that they prefer oral intake until the end.

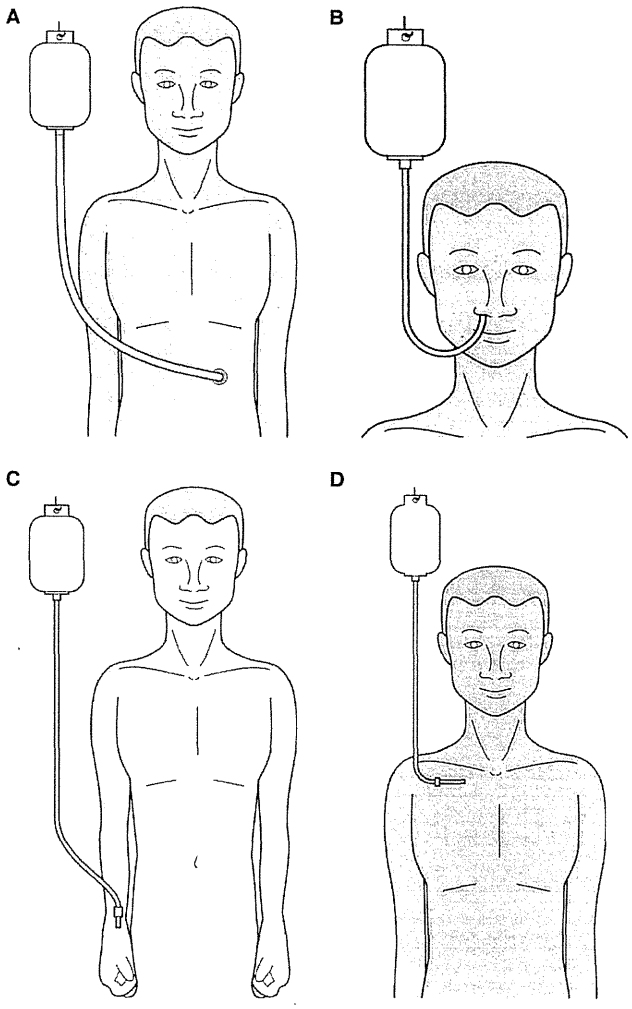

Figure 1. Types of feeding methods. (A) Percutaneous endoscopic gastrostomy. A hole is opened in the stomach using endoscopic surgery. (B) Nasal tube feeding. A tube is inserted through the nose into the stomach. (C) Drip infusion through peripheral intravenous catheter (water and limited nutrition). (D) Hyperalimentation through a central venous catheter (requires a minor surgery).

There is insufficient evidence to suggest that enteral tube feeding is beneficial in individuals with advanced dementia.[3] How should a decision regarding feeding method be made for individuals with dysphagia due to dementia? Only 4% to 5% of participants chose artificial methods as a preferred method. The Japan Geriatrics Society has established guidelines for decision-making process regarding artificial hydration and nutrition (AHN)[4] with the concept of advance care planning,[5] which emphasizes the importance of evaluation of swallowing function before introducing AHN and mentions that withdrawal, as well as administration, should be considered while respecting the well-being of

each individual; yet the guidelines have not been widely used in Japan, and mutual communication between family members while still in a healthy stage is vital to determine preference. It has been recommended that advance care planning be considered during a comprehensive geriatric assessment.[6] To respect the best interest of individuals with dementia, advance care planning should be started early on.

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PROMOTING ADVANCE CARE PLANNING DOCUMENTATION FOR VETERANS THROUGH AN INNOVATIVE ELECTRONIC MEDICAL RECORD TEMPLATE

To the Editor: Advance care planning (ACP) is increasingly recognized as an essential component of medical care.[1–3] ACP discussions should be documented in an easily accessible location for all members of the healthcare team to review so that they can guide treatment decisions. Despite the fundamental importance of ACP, most medical institutions lack effective documentation tools.[4]

Electronic medical record (EMR) reminders have been demonstrated to increase advance directive documentation,[5] but no studies have examined EMR-based ACP discussion documentation templates.[6] The goal of the current study was to examine the quality of ACP documentation after the implementation of a new Veterans Affairs (VA) EMR ACP template.

METHODS

This study was conducted at the James J. Peters VA Medical Center in Bronx, New York, a tertiary care facility with 311 authorized hospital beds and 120 nursing home beds. Study approval was obtained from the VA institutional review board.

A new template for ACP discussion documentation was implemented in the EMR in February 2009 as a part of larger quality improvement project to promote ACP documentation. This consisted of three parts: assessment of the individual's decision-making capacity; the individual's desired surrogate decision-maker; and a narrative summary of the individual's preferences regarding personal goals, values, and wishes for future medical treatment in the event of worsening health status. For individuals without decision-making capacity, the third part reflected discussions with the healthcare agent or surrogate decision-maker. Once completed, the ACP discussion note became easily accessible in the fixed, highlighted "Postings" section of the EMR face sheet (Figure 1). When ACP discussions occurred more than once for a given individual, the newest signed note automatically appeared above the previous under "Postings." The last 100 consecutive notes were reviewed.

If an individual lacked decisional capacity, the reason for incapacity was reviewed. Note content was reviewed for description about goals and values, desired place of death, and care preferences. Care preferences were divided into three categories regarding desired limitations on medical interventions (no limitation, some limitation, and comfort care only). Notes lacking documentation of healthcare preferences were also reviewed for reasons of omission.

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Detection of *Legionella pneumophila* at High Altitude in Tibetan Plateau

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INFECTION WITH LEGIONELLAE is an important cause of pneumonia known as Legionnaires' disease (LD). Legionellae are ubiquitous organisms at low altitudes (Sakamoto et al., 2009). To the best of our knowledge, however, no studies have yet reported the presence of legionellae at high altitudes. Although intense ultraviolet radiation and low temperature may effectively inhibit bacterial growth, legionellae parasitize protozoa, acquiring resistance under harmful conditions if encapsulated in protozoan cysts. To investigate whether legionellae are present at high altitudes, we collected water samples from a hot spring, puddles, streams, and tap water at altitudes from 3000 to 4200 m in Qinghai Province, China. The samples were concentrated through a 0.22-μm-pore-size membrane filter (Corning, Medfield, MA). After filtration, collected bacteria were resuspended in normal saline, mixed with an equal volume of 0.2 M KCl-HCl buffer (Muto Pure Chemicals Co., Tokyo), and inoculated onto WYOα plates (Eiken Chemical Co., Tokyo). The inoculated plates were incubated at 35°C. Smooth colonies showing a grayish white to grey-blue-purple, yellow, or green color were counted as suspicious legionellae and subcultured on *Legionella* agar (Becton-Dickinson, Mountain View, CA) supplemented with L-cysteine and ferric pyrophosphate without antibiotics. Serotyping was also performed by a slide agglutination test using commercial specific antisera (Denka Seiken, Tokyo) with a detection limit of 150 CFU/L. Real-time PCR with SYBR GreenER (Invitrogen Life Sciences, Carlsbad, CA) was also performed on water samples using the ABI Prism 7000 system (Applied Biosystems, Foster City, CA). The target primer pair was 16S rRNA (Sense primer: 5′-GCT TTCGTGCCTCAGTGTCA-3′; anti-sense primer: 5′-GCGTAGAGATCG GAAGGAAC A-3′; probe: 5′-FAM-CCAGGTAGCCGCCTTCGCCAC- TAMRA-3′) (Sato et al., 2004).

A total of 14 samples were collected, including four samples from a hot spring, four samples from puddles, three samples from streams, and three samples from tap water. *Legionella pneumophila* was isolated from three of four samples collected from the water (35°–40°C) of a hot spring at an altitude of 3930 m. This finding was not surprising, given the fact that *L. pneumophila* shows enhanced colonization at temperatures ranging from 25° to 42°C. Bacterial

TABLE 1. DETECTION OF *LEGIONELLA* SPECIES AT HIGH ALTITUDE

ID	*Sample type*	*Altitude*	*Isolation by plating method L. pneumophila serogroups*	*Gene detection by real-time PCR method Legionella species*
1	Hot spring water	3930 m	SG 3 (600 CFU/L)	65000/L
2	Hot spring water	3930 m	SG 1 (300 CFU/L)	75000/L
3	Hot spring water	3930 m	–	300000/L
4	Hot spring water	3930 m	SG1 (300 CFU/L), SG3 (900 CFU/L)	500000/L
5	Puddles	3270 m	–	57500/L
6	Puddles	3060 m	–	60000/L
7	Puddles	4180 m	–	97500/L
8	Puddles	4180 m	–	142500/L
9	Streams	3340 m	–	750/L
10	Streams	3340 m	–	Undetermined
11	Streams	3400 m	–	675/L
12	Tap water	3400 m	–	375/L
13	Tap water	3400 m	–	65000/L
14	Tap water	3400 m	–	Undetermined

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counts of the three samples were 1200 CFU/L, 600 CFU/L, and 300 CFU/L, respectively. Serotyping revealed that the samples contained *L. pneumophila* serogroups 1 and 3 (i.e., the major etiologic agents of LD) (Table 1).

L. pneumophila was not isolated from puddle, stream, or tap water samples; however, this does not confirm the absence of legionellae, as these species can exist in a viable but nonculturable state depending on the condition, re-entering a culturable state once subjected to an appropriate condition (Hussong et al., 1987). In fact, real-time PCR detected *Legionella* DNA in 12 of the 14 samples. Our results suggest a possibility that legionellae may be commonly present at high altitudes as well.

Although the presence of legionellae may not be directly linked to occurrence of LD, chronic obstructive pulmonary disease, a significant risk factor for acquiring LD, is highly prevalent among high altitude populations, possibly due to indoor air pollution caused by burning biomass fuels in confined spaces, occupational dusts, and oxidative stress (Roig et al., 1991; Basnyat et al., 2001). In travelers, differentiation between LD and high altitude pulmonary edema can be difficult, given that common symptoms of LD include fever, cough, and tachypnea. These symptoms may be exacerbated under hypoxic conditions. While early treatment with macrolides and quinolones is crucial in patients with LD, specific tests for LD are not available in most places. It is important to keep in mind that LD can occur even at high altitudes.

Author Disclosure Statement

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ORIGINAL ARTICLE

Ipsative imputation for a 15-item Geriatric Depression Scale in community-dwelling elderly people

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Abstract

Background: Missing data are inevitable in almost all medical studies. Imputation methods using the probabilistic model are common, but they cannot impute individual data and require special software. In contrast, the ipsative imputation method, which substitutes the missing items by the mean of the remaining items within the individual, is easy and does not need any special software, but it can provide individual scores. The aim of the present study was to evaluate the validity of the ipsative imputation method using data involving the 15-item Geriatric Depression Scale.

Methods: Participants were community-dwelling elderly individuals ($n = 1178$). A structural equation model was constructed. The model fit indexes were calculated to assess the validity of the imputation method when it is used for individuals who were missing 20% of data or less and 40% of data or less, depending on whether we assumed that their correlation coefficients were the same as the dataset with no missing items. Finally, we compared path coefficients of the dataset imputed by ipsative imputation with those by multiple imputation.

Results: When compared with the assumption that the datasets differed, all of the model fit indexes were better under the assumption that the dataset without missing data is the same as that that was missing 20% of data or less. However, by the same assumption, the model fit indexes were worse in the dataset that was missing 40% of data or less. The path coefficients of the dataset imputed by ipsative imputation and by multiple imputation were compatible with each other if the proportion of missing items was 20% or less.

Conclusion: Ipsative imputation appears to be a valid imputation method and can be used to impute data in studies using the 15-item Geriatric Depression Scale, if the percentage of its missing items is 20% or less.

Key words: *depression, Geriatric Depression Scale (GDS), imputation, missing data.*

INTRODUCTION

Missing data are a serious problem that can distort study results. It is an inevitable issue in almost every medical study. Among the various imputation methods, those based on statistical methods such as maximum likelihood or multiple imputation are preferred.[1] These methods generate maximum likelihood or multiple datasets to be analyzed.[2,3] However, they do not produce single values for individual items, which are necessary when we refer to individuals.

Ipsative mean imputation is a simple imputation method that is used when there is partial lack of response to items on a scale.[4–6] The individual total scale score is imputed by multiplying the average of the available item scores by the number of total items as follows:

$$\frac{(\text{the sum of responded items})}{(\text{the number of responses})} \times (\text{total number of items})$$

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Other simple methods such as hot-deck imputation have not been shown to be superior to ipsative imputation in simulation studies.[4,5] However, the validity of ipsative mean imputation has not been sufficiently evaluated.[7]

The 15-item Geriatric Depression Scale (GDS-15) is a widely used, self-administered depression questionnaire for elderly individuals that omits the non-specific physical symptoms that frequently occur among elderly populations.[8] It is important to maximize the utility of the GDS-15 in an ageing society. We have previously studied the factor structure of the GDS-15 and its relation to functional ability and quality of life (QOL).[9] In this study, we limited ourselves to data with no missingness, but then we had to give up 47% of the subjects from the analyses. We now would like to empirically examine if ipsative imputation can rescue these data.

The aim of the study was to evaluate the validity of ipsative mean imputation and to clarify the acceptable proportion of missingness for ipsative imputation in the GDS-15.

METHODS

Participants

The study was conducted in 2006 with a sample of 1660 community-dwelling elderly people aged 65 years or older from Tosa, Japan, who responded to a yearly health questionnaire. Health questionnaires were distributed by the local government and returned by mail. Included subjects were those who completed the questions about QOL and answered the GDS-15 without missing data (group_complete), those who were missing 20% of data or less (group_20miss), and those who were missing 40% of data or less (group_40miss). Figure 1 shows the inclusion process and the number in each group.

Instrument

Geriatric Depression Scale-15

The GDS-15 is a validated depression scale comprising 15 items. It was developed to exclude the effects of non-specific somatic symptoms such as anorexia and insomnia, which are frequently observed among elderly populations.[10] Each item has two possible answers (i.e. yes or no); the highest possible score is 15, which indicates the most severe depressive state. Using a cut-off of 5 points or more, the GDS-15 has a sensitivity of 97% and a specificity of 95%, compared with the results of structured clinical interviews for the determination of depression.[11]

Quality of life

Subjective QOL was assessed using a 100-mm visual analogue scale (worst QOL on the left end of the scale

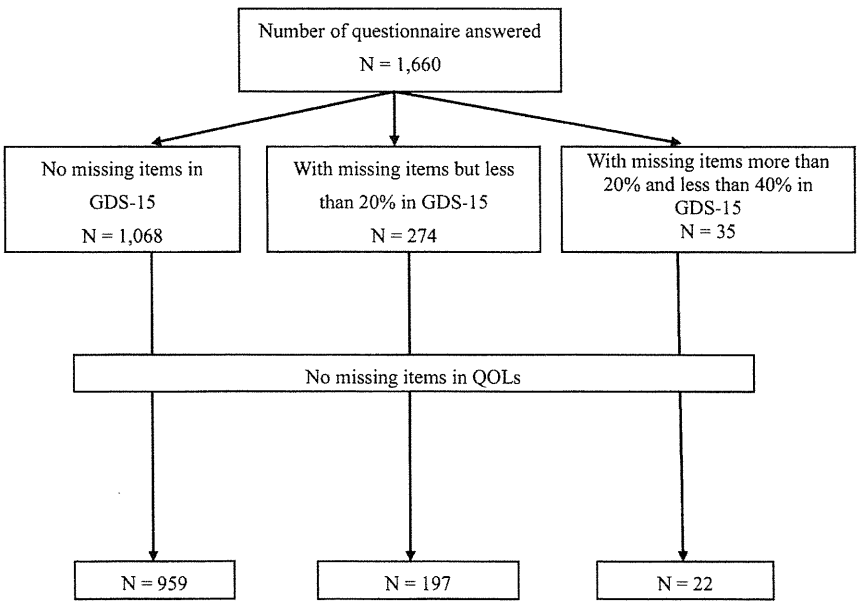

Figure 1 The inclusion process and the number in each group. GDS-15, 15-item Geriatric Depression Scale; QOL, quality of life.

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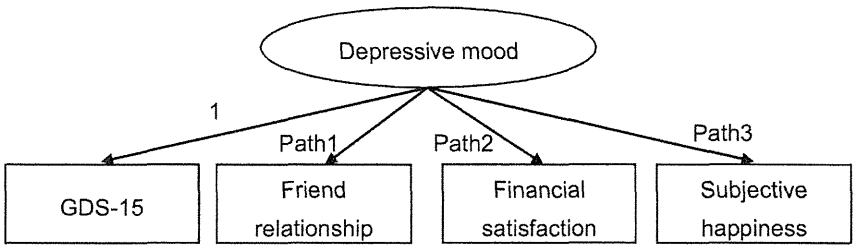

Figure 2 The model used in this study. The oval indicates a latent variable, and the rectangles indicate observable variables. GDS-15, 15-item Geriatric Depression Scale.

and best on the right) for the following three items: subjective sense of relationship with friends, financial state, and happiness.[12,13]

Model

Figure 2 shows the model used in the study. Previous studies demonstrated that depression is closely associated with QOL.[14,15] Depression was set as a latent variable, and the GDS-15 score and visual analogue scale QOL were set as observable variables affected by depression. We evaluated the validity of ipsative imputation by comparing the model fit indexes between group_complete and group_20miss as well as between group_complete and group_40miss by assuming that regression coefficients were the same or different for each pair of datasets.

Ethical consideration

The study was approved by the Ethics Committee of the Faculty of Medicine, Kyoto University, Japan (E-18). Participation in this survey was voluntary, and written informed consent was provided by each participant.

Analysis

Analysis was performed using AMOS ver. 20.0 (IBM Inc., Armonk, NY, USA).

Overall goodness of fit was assessed using the adjusted goodness of fit index, Akaike's information criterion, and root mean square error of approximation. Non-significant values of the minimum discrepancy of χ^2-based measures of discrepancy indicate that the model fit is not unacceptable. Values between 0.9 and 1.0 on the adjusted goodness of fit index indicate satisfactory goodness of fit, and values near 1.0 indicate a better model. Akaike's information criterion values show the relative goodness of the model, and lower values indicate a better model. The root mean square error of approximation represent the index of dissociation between true and model distribution, values below 0.05 indicate goodness of fit, and values over 0.1 indicate inappropriate model fit.

We first estimated structural equation models for each dataset separately and examined if the path coefficients were significantly different between the dataset with no missingness and that with some missingness. As the difference between parameters divided by an estimate of the standard error of the difference will be distributed normally, an absolute z-score above 1.96 means the parameters are different. Next, we estimated multiple-group structural equation models, and the model indexes were evaluated with and without the restriction that path coefficients of the model were the same between the dataset with no missingness and that with some missingness. Finally, we compared path coefficients of the dataset imputed by ipsative imputation to those of the dataset imputed by multiple imputation. We generated 10 datasets with Bayesian imputation in multiple imputation. Unstadardized path coefficients and their standard errors were calculated for each dataset. They were merged afterward.

RESULTS

Of the 1660 participants, those in the final analysis included 959 in group_complete, 197 in group_20miss, and 22 in group_40miss. Mean ± SD ages in each group were as follows: 75.0 ± 7.1 in group_complete, 76.3 ± 6.9 in group_20miss, and 76.6 ± 7.0 in group_40miss. Male-to-female ratios were as follows: 42:58 in group_complete, 39:61 in group_20miss, and 33:67 in group_40miss. Table 1 shows the standardized path coefficients. Depression was positively correlated with GDS score and negatively correlated with QOL. The result was the same with or without restriction. Table 2 shows the results of pairwise parameter comparison. Absolute z-scores in the comparison between group_complete and

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Table 1 Standardized path coefficients of each group

Standardized path coefficients	Group_ complete	Group_ 20miss	Group_ 40miss
Depression to GDS-15 score	0.62***	0.56***	0.79**
Depression to friend relationship	−0.58***	−0.59***	−0.77**
Depression to financial satisfaction	−0.72***	−0.77***	−0.69**
Depression to subjective happiness	−0.92***	−0.86***	−0.52*

Significantly different from zero; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. GDS-15, 15-item General Depression Scale. Group_20miss, group missing 20% of data or less; group-40miss, group missing 40% of data or less; group_complete, group missing no data.

Table 2 Z-scores of pairwise parameter comparison of path coefficients between groups

	Group_20miss vs group_complete	Group_40miss vs group_complete
Depression to friend relationship	−1.027	−0.87
Depression to financial satisfaction	−1.751	1.029
Depression to subjective happiness	−0.468	2.698†

Figure indicates the z-scores. †Z-score over 1.96 means significant difference between groups. Group_20miss, group missing 20% of data or less; group-40miss, group missing 40% of data or less; group_complete, group missing no data.

Table 3 Model fit indexes with and without restriction that paths of groups are the same

	Group_complete vs group_20miss		Group_complete vs group_40miss	
	Without restriction	With restriction	Without restriction	With restriction
Model fit indexes				
CMIN	11.314	16.896	5.563	11.341
AGFI	0.975	0.979	0.986	0.983
AIC	43.314	42.896	37.563	37.341
RMSEA	0.400	0.350	0.200	0.250

AGFI, adjusted goodness of fit index; AIC, Akaike's information criterion; CMIN, the minimum discrepancy of χ^2-based measures of discrepancy; group_20miss, group missing 20% of data or less; group-40miss, group missing 40% of data or less; group_complete, group missing no data; RMSEA, root mean square error of approximation.

group_20miss were below 1.96. However, the z-score in the comparison between group_complete and group_40miss was 2.698 in path3, meaning that path coefficients of path3 between group_complete and group_40miss were different.

Table 3 shows the model fit indexes in the analysis with and without restriction. All the model fit indexes improved in the analysis when the path coefficients were the same for group_complete and for group_20miss. However, all the model fit indexes, except for the χ^2-based measures of discrepancy, worsened when the parameters were the same for group_complete and for group_40miss. Akaike's information criterion was always smaller for the model with restriction than for that without restriction, indicating that the model fit was more parsimonious for the model with restriction.

Table 4 Comparison of unstandardized coefficients (95%confidence interval) between ipsative imputation and multiple imputation for the dataset missing 20% of data or less

	Ipsative imputation	Multiple imputation
Depression to GDS-15	1	1
Depression to friend relationship	−4.96 (−5.54, −4.38)	−4.76 (−5.33, −4.18)
Depression to financial satisfaction	−7.01 (−7.69, −6.32)	−6.77 (−7.85, −7.47)
Depression to subjective happiness	−8.00 (−8.76, −7.25)	−7.85 (−8.63, −7.07)

The parameter of the path from depression to GDS-15 was fixed at 1. GDS-15, 15-item General Depression Scale; group_20miss, group missing 20% of data or less; group-40miss, group missing 40% of data or less; group_complete, group missing no data.

We compared unstandardized path coefficients of the dataset missing 20% of data or less imputed by ipsative imputation to those by multiple imputation (Table 4). The results by ipsative imputation and multiple imputation were similar to each other; the path coefficient (95% confidence interval) from the depression to friend relationship was −4.96 (−5.54, −4.38) and −4.76 (−5.33, −4.18), depression to financial satisfaction was −7.01 (−7.69, −6.32) and −6.77 (−7.85, −7.47), and depression to subjective happiness was −8.00 (−8.76, −7.25) and −7.85 (−8.63, −7.07) by ipsative imputation and multiple imputation, respectively.

DISCUSSION

There are few studies analyzing ipsative imputation, and all of them are simulation studies that have assessed the correlation between an artificial dataset and an original one without missing values.[4–6] The present study is the first to show the validity of the ipsative imputation method and the extent to which imputation is acceptable, using a real dataset from the GDS-15.

The present study used the model fit indexes to assess the validity of the ipsative imputation method.

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The merit of using model fit indexes is that we can assess the influence of the ipsative imputation method on the meaning of the results. The present study revealed that the relationships between other variables are stable even after imputation. The high model fit indexes of the present study indicate that the ipsative mean imputation method is valid and that it does not affect the relationships between other variables. The adjusted goodness of fit indexes were over 0.9 and nearly 1.0, and root mean square errors of approximation were less than 0.1 in all groups.

The present study showed that ipsative imputation in the GDS-15 is acceptable when no more than 20% of the data is missing. Path coefficients showed no difference between group_complete and group_20miss, and model fit indexes were better with the assumption that path coefficients of group_complete were the same as those of group_20miss than with the assumption that they were different. This means that missing 20% of data or less did not influence the result. However, one path coefficient in group_complete was significantly different from that of group_40miss, and model fit indexes worsened with the assumption that path coefficients of group_complete were the same as those of group_40miss, meaning that missing more than 20% of data distorts the result. There is only one study dealing with the acceptable percentage of missing data in ipsative imputation; it also showed that respondents with missing 20% of data or less provided a good representation of the original data.[6] Along with the present study, missing 20% of items could be the threshold for using the ipsative imputation method.

Finally, we compared path coefficients of the dataset that was missing no more than 20% imputed by ipsative imputation to those imputed by multiple imputation. The results showed they were comparable each other, which strengthens the conclusion that ipsative imputation is a valid imputation method if the proportion of missing values is no more than 20%.

A limitation of this study is the relatively small sample size of group_40miss. This could lead to low model fit indexes. However, the present study at least can recommend datasets missing 20% of data or less as acceptable for using the ipsative imputation method.

The GDS-15 is a widely used scale in geriatric research, and missing data is almost unavoidable. The imputation methods using a probabilistic model are desirable, but such a model cannot represent individual data and requires special software. The ipsative imputation method is easy to use that does not require any special software. The present study indicates that the ipsative imputation method should be one of the choices for imputing data in studies using the GDS-15, if the data is missing 20% of items or less.

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