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ORIGINAL ARTICLE: SOCIAL RESEARCH, PLANNING AND PRACTICE

Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey

Minoru Takemoto,[1,2] Seijiro Mori,[3] Masafumi Kuzuya,[5] Shinya Yoshimoto,[4] Akira Shimamoto,[6] Masahiko Igarashi,[7] Yasuhito Tanaka,[8] Tetsuro Miki[9] and Koutaro Yokote[1,2]

[1]Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, [2]Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, [3]Center for Promotion of Clinical Investigation, Tokyo Metropolitan Geriatric Hospital, [4]Department of Plastic Surgery, Showa University, Tokyo, [5]Department of Community Healthcare & Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, [6]Department of Cellular and Molecular Biology, Hiroshima University Graduated School of Biomedical Sciences, Hiroshima, [7]Internal Medicine, Miyuki-Kai Hospital, Yamagata, [8]Department of Orthopaedic Surgery, Nara Medical University, Nara and [9]Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Ehime, Japan

Aim: Werner syndrome (WS) is an autosomal recessive disorder of progeroid symptoms and signs. It is caused by mutations in the *WRN* gene, which encodes a RecQ DNA helicase. The aim of this study was to revise the diagnostic criteria for Japanese Werner syndrome.

Methods: A nationwide epidemiological study was carried out from 2009 to 2011, involving 6921 surveys sent to hospitals with more than 200 beds to assess existing WS diagnostic criteria, as well as additional signs of high incidence on the basis of clinical experience with WS.

Results: The existing diagnostic criteria were reviewed, and signs with >90% incidence were listed as cardinal signs. Several criteria were added, including genetic testing and calcification of the Achilles tendon, whereas criteria that are practically difficult to obtain, such as measurement of urinary hyaluronic acid, were omitted.

Conclusion: The 26-year-old diagnostic criteria for WS were revised on the basis of the results of a nationwide epidemiological study. The proposed revised criteria will facilitate simpler, faster and more robust diagnosis of WS in the Japanese population. **Geriatr Gerontol Int 2013; 13: 475–481.**

Keywords: adult progeria, diagnostic criteria, Werner syndrome.

Introduction

Werner syndrome (WS), also known as adult progeria, is an autosomal recessive disorder caused by a mutation in the gene encoding the RecQ DNA helicase.[1,2] WS is characterized by early aging phenotypes including graying and loss of hair, juvenile cataracts, skin ulcers, insulin-resistant diabetes, premature atherosclerosis, and neoplasms.[3] The major causes of death among WS cases are malignancy and atherosclerotic vascular diseases, such as myocardial infarction.

The diagnostic guidelines of WS were released by the Research Committee on Specific Diseases-Hormone Receptor Mechanism (Dr Etsuro Ogata, Chairman) of the Ministry of Welfare of Japan in 1984;[4] however, the prevalence of WS in Japan and its diagnostic criteria have not been reviewed since. Consequently, the existing criteria do not reflect the recent progress in our understanding of WS; for example, genetic tests are not included, because the WS gene was not identified until 1996.[5,6]

The existing criteria also list the progeroid face, cataracts and scleroderma-like skin changes as cardinal signs; however, these are relatively subjective and lack specificity. Elevation of urinary hyaluronic acid is included as an objective index, but this test is cumbersome to carry out and is not specific to WS.[2,3,7] In addition, some criteria, such as a decline in the proliferative potency of skin fibroblasts, are impractical in routine clinical settings.

Washington University maintains a registry of WS cases worldwide and has proposed diagnostic criteria on

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Correspondence: Dr Koutaro Yokote MD PhD, Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Japan 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan. Email: kyokote@faculty.chiba-u.jp

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the basis of the clinical appearance of WS in all cases (http://www.wernersyndrome.org/). However, most cases of WS are Japanese individuals,[8] and ethnicity might alter the clinical features of WS. To address this issue, we initiated a nationwide epidemiological survey from 2009 to 2011 in Japan to clarify the current clinical picture among Japanese cases of WS and revise the diagnostic criteria accordingly.

Methods

Nationwide epidemiological study for WS in Japan

A nationwide epidemiological study was carried out from 2009 to 2011 consisting of 6921 primary surveys sent to hospitals with more than 200 beds. In 2011, a secondary survey questionnaire was sent to institutions that responded to the primary survey. Respondents quantified the incidences of the signs used in the existing diagnostic criteria, as well as the incidences of additional signs that were considered valuable on the basis of their clinical experience with WS.

Results

Process toward revision for new diagnostic criteria

In 2010, 3164 responses to the primary survey had been returned, which identified 396 new WS cases. Detailed clinical data were obtained in the responses to the secondary survey (Fig. 1) for 196 of these cases, consisting of 82 men, 93 women and 18 unknown.

A total of 47 cases were confirmed both clinically and genetically, whereas 146 cased were confirmed only clinically. The proportions of WS cases by decade were 62.7%, 22.7%, 10.8%, 1.1% and 0.5% for people aged in their 60s, 50s, 40s, 30s and 20s, respectively. Mean height and bodyweight were 158.3 ± 8.6 cm and 45.3 ± 8.3 kg for male patients, and 148.5 ± 8.6 cm and 3.77 ± 8.3 kg (mean ± SD) for female patients. Progeroid faces, bilateral cataracts, skin atrophy, clavus and callus, flat feet, bird-like faces, and abnormal voice were found in >85% of the confirmed cases of WS (Table 1).

Calcification in the Achilles tendon is a frequent symptom of WS

The existing diagnostic criteria for WS include many subjective or relatively non-specific symptoms. We wished to identify criteria that are more objective and are also sensitive, and included calcification of the Achilles tendon, which is frequently observed in WS, in our survey (Fig. 2); of 72 cases in which calcification of the Achilles tendon could be determined, 80% were positive. Furthermore, the segmental and flame-like patterns of calcification were highly specific to WS (Fig. 2).

New diagnostic criteria for WS

The incidences of other symptoms among cases with or without genetic diagnosis are shown in Table 1. Some symptoms were of limited diagnostic value; for example, urinary hyaluronic acid was measured in just 14 cases, and the reference range was not specified.

On the basis of these results and with unanimous agreement from the Japanese Werner Syndrome Working Committee, new diagnostic criteria (Table 2) have been formulated on the basis of the extensive clinical experience with Japanese cases of WS accumulated over many years.

Discussion

The diagnostic criteria for WS have been revised after an interval of 26 years on the basis of the results of a nationwide epidemiological study in Japan carried out during 2009–2011.

WS cases develop normally until their first decade and are usually first identified after the lack of an early adolescent growth spurt leading to the characteristic short stature and low bodyweight.[3] Both sexes are affected equally. Hair loss, graying hair, scleroderma-like skin changes, bilateral cataracts, abnormal glucose and lipid metabolism, hypogonadism, skin ulcers, and bone deformity appear by the fourth decade. Premature atherosclerosis and malignant tumors are the most common causes of death.[3] These symptoms appear chronologically after puberty; therefore, some symptoms might be absent in younger cases.

Progeroid faces, formerly a cardinal sign, have been changed to the more objective progeroid changes of hair (gray hair, hair loss, etc.). Regarding changes in hair, proper history taking is required, because white hair might be masked by hair dye or wigs.

Cataracts should be bilateral; in the present study, >75% of cases had bilateral cataracts. Acceptable changes of skin are atrophic skin, tight skin, clavus, callus or intractable ulcers. In WS cases, clavus and calluses might become intractable ulcers as shown in Figure 3; it is therefore important to make detailed observations of the skin lesions on the limbs for the diagnosis, as well as for aggressive treatment.

Calcification in the Achilles tendon is easily examined on routine X-ray and is highly sensitive for WS, and proactive X-ray images are recommended when WS is suspected. However, Achilles tendon calcification might not be present in young cases, and minute calcifications might require diagnosis by a specialist, such as an orthopedic surgeon.

☐Case1 ☐Case2 ☐Case3 ☐Case4 ☐Case5 ☐Case6

Name: _____

☐Confirmed case who regulary goes to hospital.
☐Suspicious case who regulary goes to hospital.
☐Confirmed case who has been to hospital within past 5years.

Gender ☐Male ☐Female
Age ☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown

Physical Characteristics	Presence of symptoms	Onset of symptoms
1. Height and weight		Height( )cm, Weight( )kg
2. Progeroid face		
・Gary hair and/or boldness	☐Yes ☐No ☐Unkown	
・Bird-like face	☐Yes ☐No ☐Unkown	
3. Changes of feet		
・Flat foot	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Clavus, Callus	☐Yes (☐Upper limbs/☐Lower limbs) ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐unknown
・Deformity of foot	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Intractable skin ulcers	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
4. Changes of skin		
・Atrophic skin, tight skin	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
5. Cataract	☐Yes (☐Hemilateral/☐Bilateral) ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
6. Abnormal voice (High pitched, hoarseness)	☐Yes ☐No ☐Unkown	

Signs and symptoms	Presence of symptoms	Onset of symptoms
1. Consanguinity	☐Yes ☐No ☐Unkown	
2. parenthood	☐Yes ☐No ☐Unkown	Number of children ( )
3. Menopause	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
4. Abnormal glucose metabolism		
・Impaired glucose tolerance	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Diabetes Mellitus	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
		Medication( )
5. Dyslipidemia	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・LDL cholesterol ≧140mg/dl	☐Yes ☐No ☐Unkown	Medication( )
・HDL cholesterol <40mg/dl	☐Yes ☐No ☐Unkown	
・Triglyceride ≧150mg/dl	☐Yes ☐No ☐Unkown	
6. Fatty liver	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
7. Hypertension	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
		Medication( )
8. Atheroselerotic vascular disease		
・Cerebral hemorrhage	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Cerebral infarction	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Angina pectoris or myocardial infarction.	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
・Arteriosclerosis obliterans	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown
9. Tumors (Including benign and/or malignant tumor)	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown Location of tumor, type of tumor ( )
10. Osteoporosis	☐Yes ☐No ☐Unkown	
11. Increased urinary hyaluronic acid excretion	☐Yes ☐No ☐Unkown	
12. Genetic mutation	☐Confirmed ☐No mutations ☐Not examined	Types of mutation ( )
13. Calcification of Achilles tendon	☐Yes ☐No ☐Unkown	☐10s ☐20s ☐30s ☐40s ☐50s～ ☐Unknown

【Memo】

Figure 1 A secondary questionnaire for Werner syndrome (WS) patients. Of 6921 survey sheets sent to hospitals with more than 200 beds as the primary survey, we confirmed 396 new patients. As a secondary survey in 2011, we sent questionnaires to hospitals that responded to the primary survey, and we obtained detailed clinical data for 196 cases.

Table 1 Incidence of clinical signs in genetically or clinically confirmed cases of Werner syndrome

Symptoms	Genetically confirmed ($n = 47$)	Clinically confirmed ($n = 146$)
Gray hair, loss of hair	97.9%	98.2%
Bird-like face	93.3%	97.2%
Skin atrophy	93.2%	99%
Skin ulcer	86.3%	88.5%
Clavus or callus	90.4%	92.4%
Flat foot	94.6%	84.3%
Cataract (bilateral)	97.8% (86.0%)	89.1% (75.5%)
Abnormality of the voice	82.2%	91.3%
Consanguinity	35.3%	40.6%
Parenthood	34.4%	34.4%
Impaired glucose tolerance	22.7%	15.1%
Diabetes mellitus	55.8%	70.5%
Hypertension	30.9%	37.0%
Dyslipidemia	85.4%	60.7%
LDL-C ≥140	50%	43.6%
HDL-C <40	17.2%	25.9%
TG ≥150	59.3%	55.9%
Fatty liver	50%	42.1%
Premature atherosclerosis		
Cerebral hemorrhage	2.5%	1.1%
Cerebral infarction	2.4%	4.4%
Coronary heart disease	11.1	16.1%
Arteriosclerosis obliterans	21.6	25.8%
Tumors	44.4	40.2%
Osteoporosis	60.7	66.4%
Calcification in the Achilles tendon	76.5	83.6%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerol.

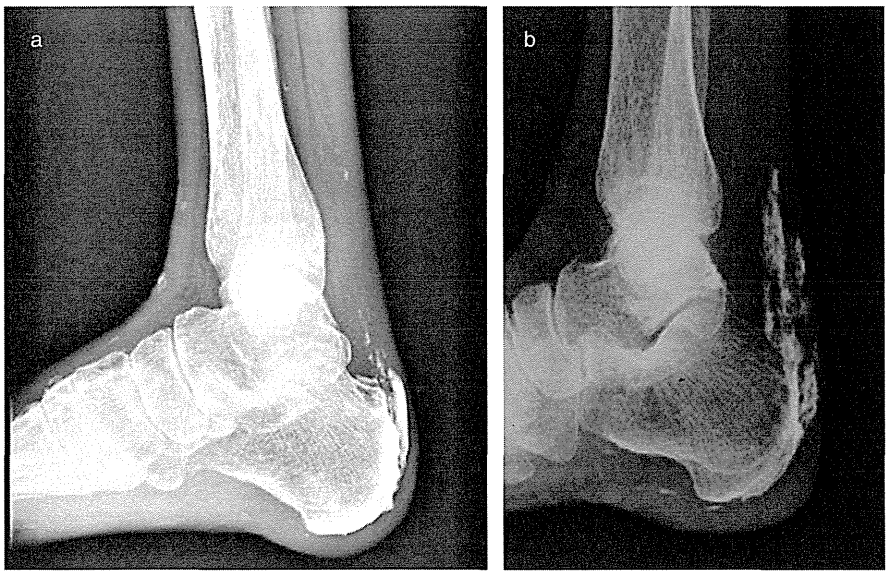

Figure 2 Calcification in the Achilles tendon seen in Werner syndrome patients. (a) Segmental and (b) flame-like calcifications in the Achilles tendon are shown.

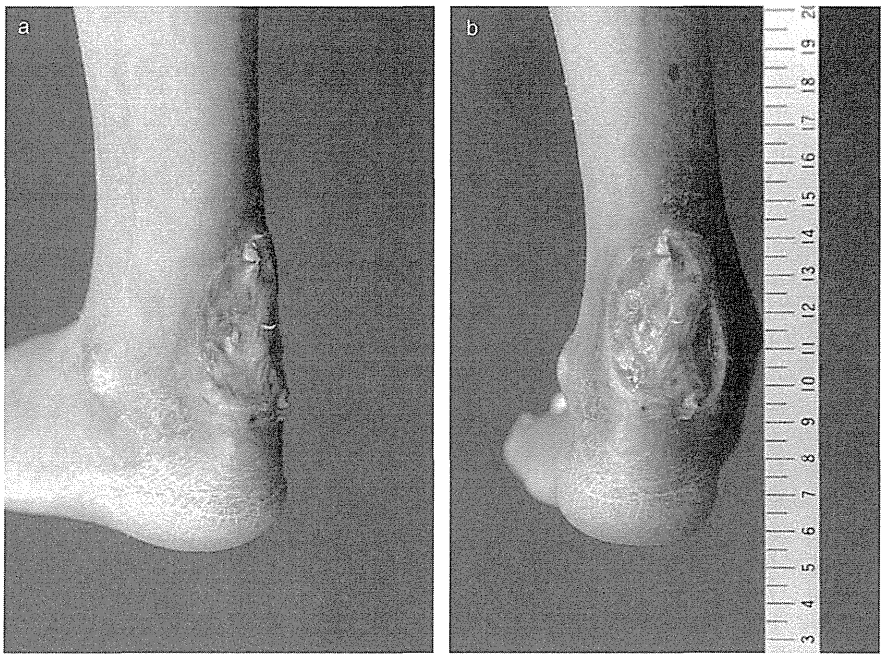

Figure 3 Skin ulcers are typically seen in Werner syndrome patients. A skin ulcer in the left Achilles tendon is shown in a 57-year-old woman.

Table 2 Revised diagnostic criteria for Werner syndrome

I. Cardinal signs and symptoms (onset over 10 until 40 years-of-age)	
1. Progeroid changes of hair	Gray hair, baldness, etc.
2. Cataract	Bilateral
3. Changes of skin, Intractable skin ulcers	Atrophic skin, tight skin, clavus, callus
4. Soft-tissue calcification	Achilles tendon, etc
5. Bird-like face	
6. Abnormal voice	High pitched, squeaky, hoarse voice
II. Other signs and symptoms	
1. Abnormal glucose and/or lipid metabolism	
2. Deformation and abnormality of the bone	Osteoporosis, etc
3. Malignant tumors	Non-epithelial tumors, thyroid cancer, etc
4. Parental consanguinity	
5. Premature atherosclerosis	Angina pectoris, myocardial infarction
6. Hypogonadism	
7. Short stature and low bodyweight	
III. Genetic testing	

Addendum: Mental retardation is seldom found in WS and cognitive function is often appropriate for the age. Confirmed: All cardinal signs are present or a gene mutation in addition to at least three cardinal signs. Suspected: Two or more cardinal signs or 1–2 cardinal signs in addition to other signs.

Because the incidence of bird-like faces is high (>93%), it is used as a cardinal sign. The characteristic WS face (Fig. 4) includes a pinched nasal bridge and diminished subcutaneous tissue.

The patient's voice might be high pitched, squeaky and/or hoarse; an example of the voice in a WS case is available on the committee website, with the patient's consent (http://www.m.chiba-u.jp/class/clin-cellbiol/werner/index.html).

Other signs and symptoms have been placed in descending order of their incidence.

Deformation and abnormality of the bone was described as osteoporosis.

Malignant tumors, which were previously only included in an addendum, are now included among the other signs and symptoms because of their high incidence and prognostic relevance. Because neoplastic lesions start developing from a young age, regular screening for malignancies is necessary for confirmed cases of WS. Epithelial and non-epithelial tumors are equally common in WS cases, in contrast to the 10:1 (epithelial : non-epithelial) ratio observed in the general

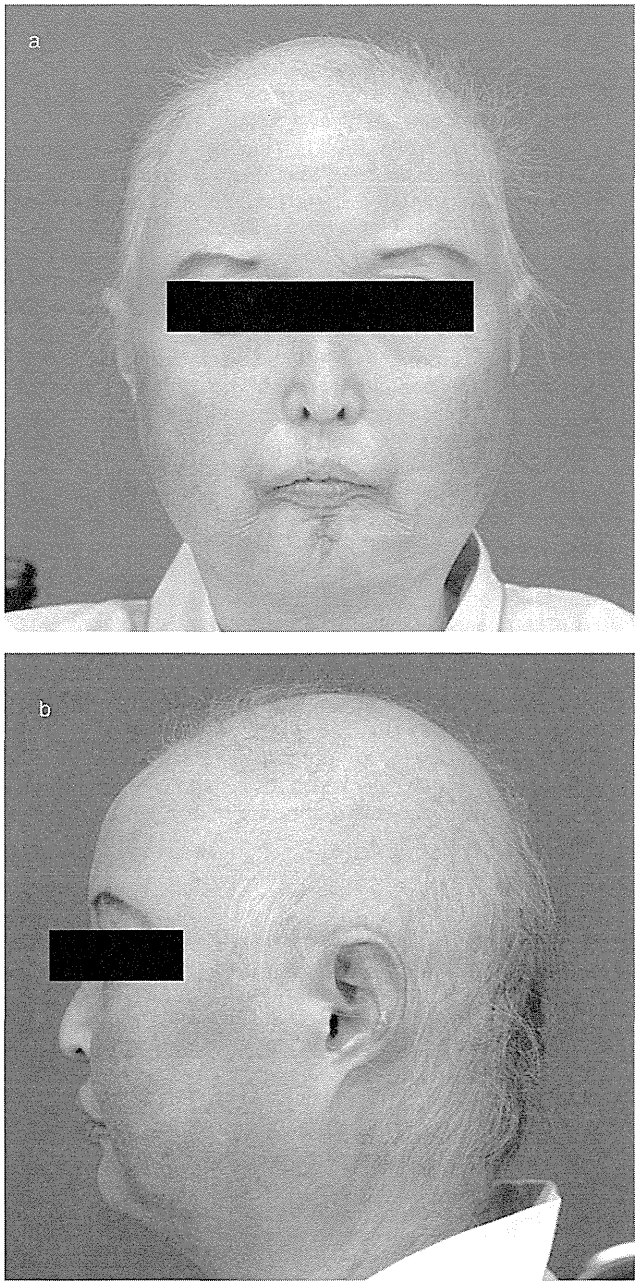

Figure 4 A bird-like face is typically seen in Werner syndrome patients. The nasal bridge of a 57-year-old woman appears pinched, and subcutaneous tissue is diminished.

population. We recently found that cancer was significantly more prevalent in diabetic cases of WS. Therefore, routine cancer screening is especially important in this particular subgroup (Onishi *et al.* manuscript submitted). Malignancy can be treated using standard regimens, because wound healing of the trunk is normal, whereas the skin and soft tissue of the extremities tend to be atrophic and delay wound healing in WS.[9]

Consanguineous marriages were found in 40% of the cases, which was lower than previously reported,[3] possibly because of increased movement among populations because of advances in transportation.

Diabetes is common in WS cases. Arteriosclerosis is of early-onset, and the incidence of ischemic heart disease and arteriosclerosis obliterans are particularly high. Because of the high possibility of silent myocardial ischemia, proactive and regular tests for arteriosclerosis are recommended for confirmed cases of WS. In contrast, morbidity because of stroke is similar to that seen in the general population of the same age in Japan.[10]

Regarding hypogonadism, it has been reported that WS is associated with secondary sexual underdevelopment, diminished fertility and testicular or ovarian atrophy. Although it was difficult to evaluate hypogonadism using the questionnaire, it is significant that less than 35% of cases in the present study had children.

On the basis of extensive clinical experience and published medical literature, cognitive function in WS cases is usually appropriate for their age, and if mental retardation is present, this is likely to be as a result of a comorbid disorder.

Genetic analysis is now included in the diagnostic criteria. *WRN* is the only gene associated with classic WS, and mutations can be identified by DNA sequence analysis[5,6,11] or western blotting[12–14] to detect aberrant forms of the protein product. Currently, these molecular genetic tests are not feasible at all institutions, and genetic testing is not essential to confirm the diagnosis of WS.

For differential diagnosis, atypical WS, which is caused by the mutation of *LMNA*;[15] mandibuloacral dysplasia,[16] which is caused by the mutation of *LMNA*;[17] Hutchinson-Gilford progeria syndrome, which is caused by the mutation of *LMNA*;[18] Rothmund-Thomson syndrome, which is caused by the mutation of *RECQ4*;[19] and Bloom syndrome, which is caused by the mutation of *RECQ2*,[20] are listed. These syndromes typically present with progeroid symptoms earlier than WS and are extremely rare in Japan.

There were some limitations to the present study. We considered the incidence of each sign in confirmed WS cases, but did not consider the incidence in the general population. Thus, the specificity of each sign has not been evaluated. Therefore, confirmed and suspected cases were specified on the basis of the results of the present study and with the consent of the Japanese Werner Syndrome Working Committee who had carried out actual clinical treatment of WS in the preceding years (Table 2).

In summary, we have revised the diagnostic criteria for WS after an interval of 26 years. We have omitted some criteria that were difficult to use in clinical settings and added criteria with more specificity, such as the calcification of the Achilles tendon, in order to make diagnosis easier and more robust. Although the genetic

basis of WS has been characterized, it remains to be determined why this defect results in the characteristic signs of WS and why these begin around puberty. The lifespan of Japanese WS cases has steadily increased by approximately 10 years.

Treatments for metabolic disorders using either HMG-CoA reductase inhibitors (statins) or peroxisome proliferator-activated receptor gamma agonists might contribute to making the prognosis of WS cases improve.[21–23] Therefore, it is important to diagnose WS early and begin treating the secondary metabolic disorders to prevent or minimize complications, such as premature atherosclerosis, and prolong the lifespan.

We hope that future research into WS will improve our understanding of its etiology, and that the diagnostic criteria will continue to be revised frequently to enable simpler, faster and more robust diagnosis.

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Disclosure statement

No potential conflicts of interest relevant to this article were reported.

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OBSERVATIONS

Sitagliptin Successfully Ameliorates Glycemic Control in Werner Syndrome With Diabetes

Werner syndrome (WS) is an autosomal recessive disorder caused by a mutation in the *WRN* gene, and it is considered to be a representative type of progeroid syndrome (1). Patients with WS often exhibit insulin resistance, which is associated with the accumulation of visceral fat and disadipocytokinemia. We and others have previously reported that pioglitazone, a peroxisome proliferator–activated receptor γ ligand, improved glycemic control and insulin sensitivity with normalization of disadipocytokine levels in patients with WS (2,3).

Here we describe a diabetic subject with WS that had good glycemic control with pioglitazone initially but worsened because of abdominal obesity and increasing visceral fat area. Sitagliptin, an inhibitor of dipeptidyl peptidase-4, was then administered, which resulted in successful improvement of glycemic control.

A 58-year-old Japanese woman with WS was admitted to our hospital with poor glycemic control. At the first visit to our hospital at 46 years of age, she exhibited graying and loss of hair, short stature, a hoarse voice, refractory skin ulcers, bilateral juvenile cataracts, dyslipidemia, and diabetes. The diagnosis of WS was confirmed by genomic DNA analysis. At that time, her height was 1.46 m, weight was 36 kg, and BMI was 15.1 kg/m^2. Her visceral fat area was 111 cm^2 (normal range, <100 cm^2 for Japanese). She was prescribed 15 mg pioglitazone daily, which resulted in stable glycemic control. Her glycated hemoglobin (HbA_{1c}) level was maintained at ~6.9% for 12 years. However, she gradually gained weight and visceral fat area (191 cm^2), which worsened her glycemic control. At the present admission, continuous glucose monitoring system (CGMS) was performed, and postprandial hyperglycemia was observed. Therefore, a 50-mg daily dose of sitagliptin was added to the pioglitazone regimen. Her laboratory parameters before and after sitagliptin administration for 6 months were as follows: fasting glucose, 122 and 110 mg/dL; 2-h postprandial glucose, 162 and 129 mg/dL; fasting C-peptide, 2.81 and 3.32 mg/dL; 2-h postprandial C-peptide, 13.99 and 11.5 mg/dL; HbA_{1c}, 7.5 and 6.5%; and mean ± SD of glucose levels detected by CGMS, 163.2 ± 32.0 and 117.1 ± 20.6 mg/dL, respectively. CGMS confirmed that sitagliptin effectively suppressed postprandial hyperglycemia.

Although patients with WS are insulin resistant, it was suggested that only those who have impaired insulin secretion develop overt diabetes (4). We were unable to observe an improvement in 2-h postprandial C-peptide levels after sitagliptin administration; nevertheless, sitaglipitin may have improved early insulin secretion in response to meals. Furthermore, sitagliptin reportedly suppresses glucagon secretion. Because hyperglucagonemia has been observed in patients with WS (5), sitagliptin may ameliorate glycemic controls at least in part via correction of dysglucagonemia.

In conclusion, we demonstrated that a single dose of sitagliptin was well tolerated in a patient with WS and diabetes, resulting in a significant improvement in glycemic control. Sitagliptin may represent an alternative choice for treatment of diabetes in patients with WS. Further studies on the use of dipeptidyl peptidase-4 inhibitor in WS with diabetes will confirm our findings.

Takumi Kitamoto, MD
Minoru Takemoto, MD, PHD
Masaki Fujimoto, MD, PHD
Takahiro Ishikawa, MD
Shunichiro Onishi, MD
Emiko Okabe, MD
Ryoichi Ishibashi, MD
Kazuki Kobayashi, MD, PHD
Harukiyo Kawamura, MD, PHD
Koutaro Yokote, MD, PHD

From the Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Chiba, Japan, and the Department of Medicine, Division of Diabetes, Metabolism, and Endocrinology, Chiba University Hospital, Chiba, Japan.
Corresponding author: Minoru Takemoto, minoru.takemoto@faculty.chiba-u.jp.
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T.K., T.I., S.O., E.O., R.I., K.K., and H.K. researched data. M.T. and M.F. wrote the manuscript and researched data. K.Y. contributed to the discussion and reviewed and edited the manuscript. M.T. and K.Y. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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LETTER TO THE EDITOR

Japanese diabetic patients with Werner syndrome exhibit high incidence of cancer

Shunichiro Onishi · Minoru Takemoto · Takahiro Ishikawa · Emiko Okabe · Ryoichi Ishibashi · Peng He · Kazuki Kobayashi · Masaki Fujimoto · Harukiyo Kawamura · Koutaro Yokote

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To the Editor

Diabetes is associated with the occurrence and progression of malignant tumors [1, 2]. Werner syndrome (WS), an autosomal recessive disorder classified as a progeroid syndrome, occurs because of mutation of the WRN gene encoding a RecQ-type DNA helicase. Because WS patients often have diabetes and malignant tumors, we initiated a nation-wide epidemiological survey in Japan to clarify the current relationship between the prevalence of diabetes and malignant tumors in them.

We sent 6921 survey sheets to hospitals with >200 beds. This survey confirmed 336 new WS patients; detailed clinical data were obtained for 163 patients with diabetes, malignant tumors, or both [3]. These patients were categorized as diabetic ($n = 102$) and non-diabetic ($n = 61$). The correlation between diabetes and epithelial tumors (cancers) or non-epithelial tumors was examined using the chi-square test.

The proportions of patients grouped according to age were 1.2, 9.8, 23.3, 62.6, and 1.8 % for patients in their 20s, 30s, 40s, 50s, and 60s, respectively. The prevalence of cancers and non-epithelial tumors was 11.7 and 19.0 %, respectively. No significant difference was observed in the morbidity rates of non-epithelial tumors in diabetic or non-diabetic patients (21.6 vs. 21.3 %, $p = 0.485$). However, diabetic patients showed significantly higher cancer prevalence than non-diabetic patients (16.6 vs. 4.9 %, $p = 0.013$). The types of malignant tumors in these patients and their prevalence rates are shown in Table 1.

The prevalence of non-epithelial tumors and cancers is similar in WS patients [4]; non-epithelial tumors are seldom observed in the general population. Insulin resistance is related to the high cancer prevalence in diabetic patients [5]. Diabetes in WS patients is usually caused by high insulin resistance [6], which may contribute to cancer development. WS patients usually die in their 40s [4]. However, in our study, more than 60 % WS patients were in their 50s, which confirmed that the average life expectancy of Japanese WS patients has increased by 5–10 years. Because cancer incidence has increased with age, aging may be a risk factor for cancer development, especially in diabetic WS patients.

Thus, our results demonstrate that diabetic WS patients show high cancer prevalence. It is therefore important to monitor the development of not only non-epithelial tumors but also cancers in these patients, especially when WS is complicated with diabetes.

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S. Onishi · M. Takemoto (✉) · T. Ishikawa · E. Okabe · R. Ishibashi · P. He · K. Kobayashi · M. Fujimoto · H. Kawamura · K. Yokote
Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan
e-mail: minoru.takemoto@faculty.chiba-u.jp

S. Onishi · M. Takemoto · T. Ishikawa · E. Okabe · R. Ishibashi · K. Kobayashi · M. Fujimoto · H. Kawamura · K. Yokote
Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan

Table 1 The types of malignant tumors in a sample of 163 Japanese Werner syndrome patients with or without diabetes

		DM ($n = 102$)	Non-DM ($n = 61$)	p value
Epithelial tumors (cancers)	Thyroid cancer	3 (2.9 %)[a]	1 (1.6 %)[b]	
	Pharyngeal cancer	1 (1.0 %)	0	
	Lung cancer	3 (2.9 %)	0	
	Breast cancer	1 (1.0 %)	1 (1.6 %)	
	Gastric cancer	2 (2.0 %)	0	
	Hepatic cancer	2 (2.0 %)	0	
	Pancreatic cancer	2 (2.0 %)	0	
	Renal cancer	1 (1.0 %)	0	
	Bladder cancer	0	1 (1.6 %)	
	Colon cancer	1 (1.0 %)	0	
	Uterus cancer	1 (1.0 %)	0	
		17 (16.6 %)	3 (4.9 %)	0.013
Non-epithelial tumors	MFH	2 (2.0 %)	4 (6.6 %)	
	Leiomyosarcoma	1 (1.0 %)	1 (1.6 %)	
	MPNST	1 (1.0 %)	0	
	Osteosarcoma	1 (1.0 %)	1 (1.6 %)	
	Melanoma	4 (3.9 %)	2 (3.3 %)	
	Meningioma	3 (2.9 %)	3 (4.9 %)	
	MDS	3 (2.9 %)	1 (1.6 %)	
	MM	2 (2.0 %)	0	
	Others	5 (4.9 %)	1 (1.6 %)	
		22 (21.6 %)	13 (21.3 %)	0.485

The correlation between the prevalence of epithelial tumors (cancers) and non-epithelial tumors and diabetes using the chi-square test was examined

MFH malignant fibrous histiocytoma, *MPNST* malignant peripheral nerve sheath tumor, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *DM* diabetes mellitus

[a] Number (ratio among DM)

[b] Number (ratio among non-DM)

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Author Contributions: Chang Won Won: study concept and design, preparation of manuscript. Hwan-Sik Hwang: acquisition of subjects and data, preparation of manuscript. Both authors approved the final version.

Sponsor's Role: None.

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INCIDENCE AND CHARACTERISTICS OF METABOLIC DISORDERS AND VASCULAR COMPLICATIONS IN INDIVIDUALS WITH WERNER SYNDROME IN JAPAN

To the Editor: Werner syndrome (WS) is an autosomal-recessive disorder caused by a mutation of the WNR gene and is considered to be a representative type of progeroid syndrome,[1] which is highly prevalent in Japan. Because individuals with WS often have metabolic disorders and vascular complications, a nationwide epidemiological survey was initiated in Japan to clarify the current relationship between the prevalence of metabolic disorders and vascular complications in these individuals.

The primary survey involved sending 6,000 survey sheets to hospitals with more than 200 beds. This survey confirmed 336 new patients. The secondary survey in 2011 involved sending questionnaires to hospitals that had responded to the primary survey. Detailed clinical data were obtained for 185 cases. Complication rates of metabolic disorder and morbidity from complications in individuals with WS were compared with those in the average Japanese population.

Of the 185 patients, 86 were men, 98 were women, and the sex of one was unknown. The proportions of patients were 62.7% aged 50 to 59, 22.7% aged 40 to 49, 10.8% aged 30 to 39, 1.1% aged 20 to 29, and 0.5% aged 60 to 69, respectively. Mean height and body weight were 158.3 ± 8.6 cm and 45.3 ± 8.3 kg for 44 male patients and 148.5 ± 8.6 cm and 37.7 ± 8.3 kg for 94 female patients. The prevalence of diabetes mellitus and abnormal glucose tolerance were 55.7% and 6.5%, respectively, with a total combined rate of 62.2% (Table 1). Drugs used for diabetes mellitus included pioglitazone (10.3%), sulfonylurea (7.6%), insulin (7.0%), alpha-glucosidase inhibitor (5.9%), and metformin (4.9%). The morbidity of hyperlipidemia was 51.6%. Treatments for hyperlipidemia included statins (18.4%), fibrates (5.4%), and others (3.8%). The morbidity of hypertension was 25.9%, lower than that of the average Japanese population (Table 1). Therapeutic agents used were angiotensin II receptor antagonists (4.9%) and calcium blockers (4.3%).

Morbidities of vascular diseases in WS were 1.1% for brain hemorrhage, 2.7% for cerebral infarction, 10.3% for angina pectoris or myocardial infarction, and 17.3% for arteriosclerosis obliterans. Individuals with WS were divided into two groups (with (n = 45) and without vascular disease (n = 140)), and correlations with diabetes mellitus ($\chi^2 = 4.24$, $P = .04$), hyperlipidemia ($\chi^2 = 7.90$, $P = .005$), and hypertension ($\chi^2 = 11.16$, $P < .001$) were examined, with a critical value of 3.84, confirming that metabolic disorders are closely related to vascular disease.

This study confirmed a considerably higher prevalence of metabolic disorders and cardiovascular diseases in Japanese with WS than in the average Japanese population (Table 1). Because of the high prevalence of metabolic disorders, the accumulation of visceral fat tissue in WS has been attributed to the development of the metabolic syn-

Table 1. Morbidity from Metabolic and Atherosclerotic Diseases in Individuals with Werner Syndrome and the General Japanese Population

Complication	Individuals with Werner Syndrome, n (%)			General Japanese Population Aged 50–59 (%)
	Total (n = 185)	Male (n = 86)	Female (n = 98)	
Diabetes mellitus	115 (62.2)	45 (69.2)	73 (61.4)	10.2*
Hypertension	48 (25.9)	17 (38.6)	31 (33.0)	47.2*
Dyslipidemia	94 (51.6)	27 (41.5)	61 (51.7)	16.4*
Low-density lipoprotein cholesterol ≥ 140 mg/dL	42 (22.7)	13 (29.5)	28 (28.6)	
High-density lipoprotein cholesterol < 40 mg/dL	18 (9.7)	7 (15.9)	10 (10.2)	
Triglycerides ≥ 150 mg/dL	58 (31.4)	16 (36.4)	41 (41.8)	
Atherosclerotic diseases				
Cerebral vascular diseases	7 (3.8)	5 (5.8)	2 (2.0)	2.04†
Cardiovascular diseases	19 (10.3)	9 (10.5)	10 (10.2)	0.73†

Data from Ministry of Health, Labor, and Welfare in *2006 and †2008.

drome,[2] but the mechanisms underlying the accumulation of visceral fat tissue frequently observed in WS remains largely unknown.

With regard to the characteristics of vascular disease in WS, the morbidity rate of stroke in individuals with WS was similar to that in the general Japanese population of the same age, although individuals with WS have a considerably greater prevalence of metabolic disorders. Stroke is more commonly caused by arteriolosclerosis than by atherosclerosis. Furthermore, arteriolosclerosis in the brain is associated with changes characterized by hyalinization of the tunica media or fibrinoid necrosis, which are closely associated with hypertension. The present survey demonstrated that the occurrence of hypertension as a complication of WS was lower than in the general Japanese population of the same ages; this has been a contributing factor to the smaller number of cerebral vascular disease in individuals with WS. In accordance with this lower incidence of cerebral vascular disturbances in individuals with WS, the function of the central nervous system is known to be maintained at a normal level, together with a lower incidence of dementia. Although the cause has not been clarified, the difference between the distribution of RecQ-type helicase (a protein that is mutated in WS) in vascular and cerebral blood vessels may be responsible. Furthermore, rapid cell division is associated with telomere stability, which is also associated with the WS protein.[3] Therefore, central nerves undergoing fewer cell divisions may be associated with a small number of disorders.

In conclusion, the frequency of stroke was lower in WS despite these individuals having numerous risk factors. A mutation in the WNR gene has been suggested as a possible protective process against the development of stroke. This finding may be significant for understanding the mechanism of the pathogenesis and progression of stroke, as well as for developing new therapeutic methods.

Emiko Okabe, MD
Minoru Takemoto, MD, PhD
Shunichiro Onishi, MD
Takahiro Ishikawa, MD
Ryouichi Ishibashi, MD
Peng He
Kazuki Kobayashi, MD, PhD
Masaki Fujimoto, MD, PhD
Harukiyo Kawamura, MD, PhD
Koutaro Yokote, MD, PhD
Department of Clinical Cell Biology and Medicine
Graduate School of Medicine, Chiba University
Chiba, Japan

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Emiko Okabe: analysis and interpretation of data, preparation of manuscript. Minoru Takemoto: study concept and design, analysis and interpretation of data, preparation of manuscript, acquisition of subjects and data. Shunichiro Onishi, Takahiro Ishikawa, Ryouichi Ishibashi, Peng He, Kazuki Kobayashi, Masaki Fujimoto, and Harukiyo Kawamura: acquisition of subjects and data. Koutaro Yokote: study concept and design; preparation of manuscript.

Sponsor's Role: None.

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COMMENTS/RESPONSES

REHABILITATION OF ELDERLY ADULTS WITH SEVERE COGNITIVE IMPAIRMENT: IT IS TIME FOR EVIDENCE

To the Editor: The article by Poynter and colleagues[1] adds important information to the growing body of literature on the rehabilitation of older adults with dementia. This topic has several important clinical, organizational, and economic implications. In recent years, an increasing number of reports have shown that the rehabilitation of this group of individuals is not only possible and feasible, but is also clinically relevant. People with dementia and hip fracture[2] and other nonspecific medical conditions have been successfully rehabilitated in various studies, despite the severity of their cognitive impairment.[1,3] Furthermore, unconventional and technology-based techniques are now promising strategies to overcome the gap of cognitive impairment in these individuals.[4,5]

Despite these positive remarks, motor rehabilitation of older adults with dementia is far from being an evidence-based discipline. A crucial question is the lack of randomized clinical trials, which are the only way to draw definite conclusions about the effectiveness of rehabilitation in individuals with dementia. For instance, in the field of hip fracture rehabilitation—a topic expected to become prominent in the coming years given the progressive aging of the population[6]—there are only two randomized clinical trials including individuals with dementia.[7,8] Of these, only one,[8] a small subgroup analysis of a previous multicomponent clinical trial to reduce postoperative delirium in elderly adults with hip fractures,[9] used a definition of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.

The results of randomized controlled studies in individuals with dementia will provide important information to physicians and policy-makers to dedicate adequate

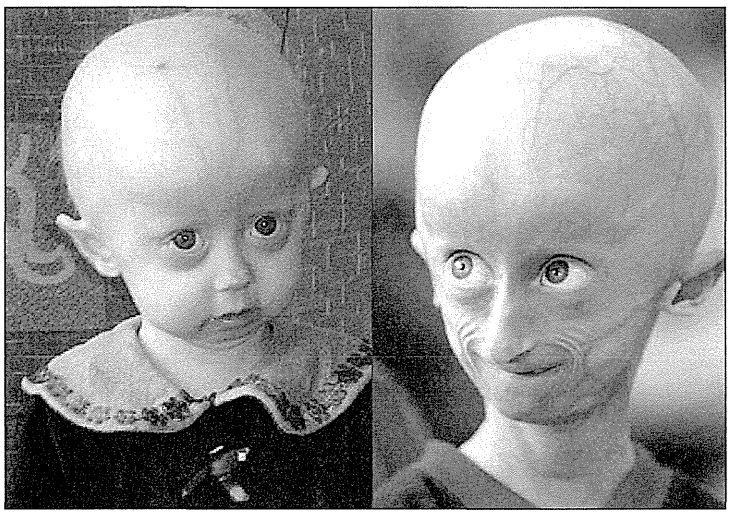
Ⅳ. 参考資料

参考資料　目次

こんな患者さんはいませんか?

ハッチンソン・ギルフォード・プロジェリア症候群

・低身長・低体重
・大きな頭部、カギ鼻などの小人症様の外形
・皮膚老化、脱毛、糖尿病、動脈硬化などの早老性変化が顕著



【 特　徴 】

・新生児期ないし幼児期（生後 6 ヶ月～ 24 ヶ月）に好発し、全身の老化が異常に進行する**早老症候群**
・非常に稀な（400 ～ 800 万人に 1 人）、散発性常染色体優性の症候群であり、ラミン A（LMNA）遺伝子の変異による。
・低身長および低体重を引き起こす成長障害がある。
・特徴的な頭蓋顔面異常（前額突出、小顎症、目の異常突出および／または小さい「くちばし状の」鼻が含まれる）がある。
・高コレステロール血症、糖尿病、骨粗鬆症、白内障、白髪などの早老変性が顕著
・動脈硬化が早期から進行し、多くの場合、13 歳頃に心筋梗塞や脳卒中によって死に至るが、成人例も報告されている。
・精神発達は正常

参考資料①

ハッチンソン・ギルフォード・プロジェリア症候群 全国疫学調査

有病者数全国一次調査用紙

施設 No.

1173

記載者御氏名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

記載年月日：2013 年＿＿＿月＿＿＿日

「1. なし」もしくは、「2. あり」のどちらかに○をお付け下さい。
※「2. あり」の場合は、患者症例数をご記載下さい。

■ハッチンソン・ギルフォード・プロジェリア症候群「確定」患者

1. なし　　2. あり　　[男＿＿＿＿例；女＿＿＿＿例]

■ハッチンソン・ギルフォード・プロジェリア症候群「疑い」患者

1. なし　　2. あり　　[男＿＿＿＿例；女＿＿＿＿例]

【記入上のお願い】

1. ラミン A（LMNA）遺伝子の異常が確定している患者さんは「確定」患者の欄に、臨床症候のみの場合は「疑い」患者の欄にご記入ください。
2. 貴診療科において、過去 10 年間に経験された症例に関してご記入下さい。
3. 全国における有病患者数の推計を行いますので、該当患者がない場合でも「1. なし」に○をつけ、ご返答下さい。
4. 症例をご経験の施設には、後日、第 2 次調査をお願いしたく存じます。その際はご協力のほどお願い申し上げます。
5. ご住所等に誤まりがございましたら、お手数ですがご訂正をお願い致します。

2013 年 2 月 28 日までに、ご返送下さいますようお願いします。

ハッチンソン・ギルフォード・プロジェリア症候群（二次調査用紙）

症例者1名（1症例）につき、用紙1枚となります。
※複数の症例者が確認されている場合、お手数ではございますが、この用紙をコピーし、症例欄にチェックを入れ、ご記載頂けますようお願い申し上げます。

施設/診療科名：千葉大学医学部附属病院　内科

001-9999-99

症例欄
□症例1　□症例2　□症例3　□症例4　□症例5　□症例6

記載者御氏名：

□現在通院中の患者である
□疑いがある患者である
□過去5年以内に通院された患者

症例者の性別	症例者の最終診察時の年齢
□男性	（　　）歳
□女性	亡くなっている場合は、死亡時の年齢（　　）歳

身体的特徴		徴候の有無	発症年齢
1. 身長及び体重			身長（　　）cm　体重（　　）kg
2. 早老様顔貌	・白髪または脱毛	□あり　□なし　□不明	
	・前額突出・小顎症	□あり　□なし　□不明	
	※目の異常突出および または小さい「くちばし状」鼻		
3. 皮膚の変化	・萎縮	□あり　□なし　□不明	（　　）歳
	・潰瘍	□あり（□上肢/□下肢） □なし　□不明	（　　）歳
4. 足の変化	・鶏眼や胼胝	□あり　□なし　□不明	（　　）歳
	・扁平足	□あり　□なし　□不明	（　　）歳
	・足趾の変形	□あり　□なし　□不明	（　　）歳
5. 白内障		□あり（□片側/□両側） □なし　□不明	（　　）歳

徴候と所見		徴候の有無	発症年齢
1. 血族結婚		□あり　□なし　□不明	
2. 月経の有無		□あり　□なし　□不明	（　　）歳
3. 糖代謝異常	・境界型糖尿病	□あり　□なし　□不明	（　　）歳
	・糖尿病	□あり　□なし　□不明	（　　）歳
			使用薬剤名（　　）
4. 脂質異常症		□あり　□なし　□不明	（　　）歳
初診時もしくは治療前	・LDLコレステロール≧140mg/dl	□あり　□なし　□不明	使用薬剤名（　　）
初診時もしくは治療前	・HDLコレステロール＜40mg/dl	□あり　□なし　□不明	
初診時もしくは治療前	・中性脂肪≧150mg/dl	□あり　□なし　□不明	
5. 脂肪肝		□あり　□なし　□不明	（　　）歳
6. 高血圧		□あり　□なし　□不明	（　　）歳
			使用薬剤名（　　）
7. 動脈硬化性疾患	・脳出血	□あり　□なし　□不明	（　　）歳
	・脳梗塞	□あり　□なし　□不明	（　　）歳
	・狭心症または心筋梗塞	□あり　□なし　□不明	（　　）歳
	・閉塞性動脈硬化症	□あり　□なし　□不明	（　　）歳
8. 腫瘍性病変（良性・悪性を含む）		□あり　□なし　□不明	（　　）歳
			腫瘍性病変の部位、種類（　　）
9. 骨粗しょう症		□あり　□なし　□不明	使用薬剤名（　　）
10. 尿中ヒアルロン酸の増加		□あり　□なし　□不明	
11. 遺伝子変異（LMNA変異）		□確定済み □変異なし　□未検査	確定済みの場合は、遺伝子変異の部位（　　）
		※確定されていない場合は、当研究班において無料で検査を致します。　□希望する　□希望しない	
12. 尿蛋白の有無		□あり　□なし　□不明	

【自由記入欄】※その他使用歴のある薬剤がございましたらご記載下さい（成長ホルモンなど）

※ご不明な点がございましたら、ご相談下さい。

（参考資料３）

医療ルネサンス　No.5700　難病とともに　診療のいま　6/6

見過ごされる患者も

足が不自由な石井さん（右）だが、夫のサポートで患者会活動に参加するなど明るく暮らしている

「これまでのいろいろな症状は、この病気が原因で起こっていたということが初めて理解できました」

ウェルナー症候群の患者で、東京都江戸川区の主婦、石井奈津子さん(55)は2011年、この病気を専門的に研究する医師に出会った時のことを振り返る。

10年ほど前、右足のアキレス腱が切れて入院したが、傷口が細菌感染し、膝下を切断。その後、今度は左足に潰瘍ができ、かかとから先を切った。

ウェルナー症候群は、思春期以降、急速に老化が進む遺伝子疾患。原因不明で、根本的な治療法はない。40歳くらいまでに白内障になったり、皮膚が萎縮してひどい潰瘍ができたりする。患者はがんや糖尿病になりやすい傾向もある。

石井さんも、治療の過程でウェルナー症候群とは聞いていたが、どのような病気なのか、どんな症状を引き起こすのかといったことについて、「詳しい先生がいなくて、わかりやすい説明はありませんでした」。医師も本人も、目の前の症状への対処に精いっぱいだったということもある。

この病気の治療で実績のある千葉大病院（千葉市）で、足の血流を良くする血管の手術を受けるなどした石井さんは、病状がやや改善。同病院と自宅近くの病院で通院治療を続けている。

この病気の患者は国内に推定2000人とそもそも少ないが、確認できている患者は疑い例も含め約400人に過ぎない。多くが診断されず見過ごされているとみられている。

「適切な診断基準を広め、一番いい診療をどこでも受けられるように標準化したい」と、同大教授（細胞治療内科学）の横手幸太郎さんは話す。横手さんらの研究班は12年、診断と診療の指針をまとめた。

それまで参考にされてきた「診断の手引き」は1984年に作られたもので、後に可能になった遺伝子診断が含まれていないなどの問題があった。

指針は、この手引きを改善したもので、例えば、アキレス腱の付け根が硬くなる「石灰化」という状態が主な兆候の一つに加えられた。これは患者の8割に見られる症状で、エックス線画像で客観的に確認できる。

横手さんによると、90年代まで、この病気の患者は平均40代半ばで亡くなっていたが、2000年代になると平均50代半ばまで延び、中には60代を迎えた患者もいた。

横手さんは「適切な診療で病状の改善はできる。潜在的な患者を見つけ、支援することが必要です」と訴えている。

（高梨ゆき子）

（次は「脱・短命県」です）

医療・健康情報はインターネットサイト「ヨミドクター」（http://yomidr.jp）で

くらし■家庭

（参考資料４）

【患者家族の会　活動実績】

・2013年6月5日　第5回患者会ウェルナー症候群患者・家族の会「George M. Martin先生を囲んで」　大阪国際会議場

・2013年10月20日近畿・中部地区集会～愛知県名古屋市（ウィルあいち）

・2013年10月19日九州地区集会～福岡県福岡市(ホテルセントラーゼ博多 ザ・ラウンジ)

・2013年10月14日中国地区集会～広島県広島市（広島大学）

・2013年10月13日関東地区集会～千葉県（千葉大学病院第2講堂）

・2012年12月22日近畿・中部地区集会～愛知県名古屋（ウィルあいち）

・2012年10月16日　九州地区集会～福岡県（ホテルセントラーゼ博多 ザ・ラウンジ）

・2012年7月8日関東地区集会～千葉県（千葉大学病院第2講堂）