



Review Article

Nationwide survey of Cockayne syndrome in Japan: Incidence, clinical course and prognosis

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Abstract In the first nationwide survey of Cockayne syndrome (CS) in Japan, the incidence of CS was estimated to be 2.77 per million births (95%CI: 2.19–3.11) and the prevalence was approximately 1 in 2 500 000. A total of 47 CS patients (24 surviving and 23 deceased) were identified. Based on clinical course, these 47 patients were classified into CS type 1 (n = 41; 21 surviving, 20 deceased), CS type 2 (n = 2; all deceased), CS type 3 (n = 3; all surviving), and CS/xeroderma pigmentosum type D (n = 1, deceased). In the 41 CS type 1 patients, seven findings (i.e. failure to thrive; photosensitivity; deafness; characteristic facial appearance of CS [sunken eyes]; foot joint contracture; intellectual disability; and basal ganglia calcification on computed tomography [CT]) were observed in >90% of patients. Of these, failure to thrive, photosensitivity, and intellectual disability (language delays) developed before 2 or 3 years of age, whereas deafness, sunken eyes, and basal ganglia calcification on CT occurred later. Features such as bodyweight and height stagnation, language delay, abnormal nutritional pathways (tube feeding), and renal failure were more prominent in the 20 deceased CS type 1 patients than in the 21 surviving CS type 1 patients. Of the 20 deceased CS type 1 patients, nine developed severe renal failure during the terminal stages of their condition. The present findings suggest that the clinical course of CS includes a diverse range of symptoms, but each type has characteristic symptoms. In addition, the management of renal failure and nutrition are very important for ensuring good quality of life throughout the long-term course of CS.

Key words Cockayne syndrome, incidence, renal failure, subtype.

Cockayne syndrome (CS) is a rare autosomal recessive disorder caused by deficient nucleotide excision repair. It is characterized by poor growth and progressive multisystem dysfunction, which also affects the central nervous system. Cockayne reported the cases of two siblings in a paper entitled “Dwarfism with retinal atrophy and deafness” in 1936,¹ and 10 years later he reported follow-up data for the same patients, which indicated that the siblings had suffered progressive hearing loss, visual dysfunction, and joint contracture.² In 1977, Sugarman *et al.* described eight major findings of CS (dwarfism; intellectual disability; microcephaly; ataxia; retinal pigmentation; neural deafness; progeroid features; and intracranial calcification) and seven minor findings (photosensitivity; kyphosis; ankylosis; optic atrophy; carious teeth; large, cold hands and feet; and hypogonadism).³ Schmickel *et al.* showed that fibroblasts from two unrelated CS patients had increased sensitivity to UV irradiation, but not X-ray irradiation, as evaluated on colony-forming ability, although both cell lines had normal

thymidine dimer removal rates.⁴ This suggested that an enzymatic defect in the repair of UV light-induced damage might be involved in CS. Mayne and Lehmann showed that Cockayne cells failed to recover their ability to synthesize RNA after UV irradiation despite normal excision and daughter-strand repair pathways, indicating that the recovery of RNA synthesis is an important early response to UV irradiation.⁵ This key finding is used as a cellular diagnostic test for CS. Extensive research has since clarified that mutations in the *ERCC6* (*CSB*) or *ERCC8* (*CSA*) genes, which are involved in DNA repair, are closely related to the pathogenesis of CS. Mutations in the *CSB* or *CSA* gene compromise transcription-coupled repair and resumption of the replication and transcription of damaged DNA, nuclear DNA, and mitochondrial DNA. The relationships between the presence/absence of *CSA* and *CSB* gene mutations and the various types of CS, however, are complex.

Cockayne syndrome is classified into three types based on age of onset, symptom severity, and rate of progression: CS type 1, the classic form; CS type 2, a severe form; and CS type 3, a late-onset milder form.⁶ Some cases involve a combination of the symptoms of CS and xeroderma pigmentosum (CS/XP). Natale proposed a revised CS classification including a fourth group, UV sensitivity only/adult onset.⁷ Although some cases involve broader phenotypic variation and a mixture of the features of different types of CS, the present simple classification, which was

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adopted in the present study, is still useful for prognostic evaluation. CS is usually diagnosed based on clinical features, neuroimaging, and neurophysiological tests, although cytological and genetic diagnostic approaches have been extensively investigated.

Although the incidence rates of DNA repair disorders including CS have been reported in Western Europe,⁸ no data regarding the incidence of CS in Japan are available. In addition, it is necessary to understand the regional distribution of the condition. In 2009, we founded a research group examining CS in Japan to clarify the current clinical status of the condition and to develop support guidelines for it.

In the present review, we first describe the findings of the first nationwide survey of CS to be conducted in Japan, which was performed to clarify the incidence rate and current clinical status of CS. In addition, we present representative cases in order to clarify the detailed course of each type of the condition, and relevant findings from review of the literature. Furthermore, we describe the neuropathological findings of CS and the role of oxidative stress involved in the condition in an attempt to clarify the pathogenesis of CS. The study was approved by the ethics committee of Tokyo Metropolitan Institute of Medical Science.

Methods

Questionnaires were sent to pediatricians, child neurologists, and rehabilitation physicians responsible for CS patients.

Questionnaires were sent to a total of 921 institutions including certified postgraduate clinical training institutions (Department of Pediatrics, 733 institutions), children's hospitals (Department of Child Neurology, 18 institutions), and rehabilitation centers for children with disabilities (Department of Pediatrics, 170 institutions).

We sent the first questionnaire to 921 hospitals in order to ascertain the respondents' experience of CS. We sent the second questionnaire to the institutions that replied to the first questionnaire and had encountered CS patients in order to request more detailed clinical information, that is, current patients, past patients (those who no longer attended the clinic), and deceased patients.

The second questionnaire included questions about gender, date of birth, family history of the disorder, perinatal data, growth, facial appearance, psychomotor development, neuroimaging findings, hearing and visual loss, neurophysiological data, photosensitivity, renal and hepatic function, anemia, involuntary movements, and nutritional status, and so on. CS was mainly diagnosed based on clinical symptoms and neuroimaging findings, and genetic tests were not necessarily required.

Results

Primary survey

Of the 921 institutions targeted, 674 responded to the first questionnaire, resulting in a response rate of 73.2%. Of these, 45 institutions reported that they had experience of diagnosing or treating patients with CS ($n=76$). The 76 patients included 37 surviving and 39 deceased patients.

Secondary survey

Of the 45 institutions that had encountered CS patients, 28 provided detailed clinical information about their CS patients ($n=48$). To avoid patient duplication, we searched for patients with overlapping demographic details (gender, date of birth, place of residence, and clinical course). After excluding suspected duplicates, a total of 47 CS patients (24 surviving and 23 deceased) were identified. Based on clinical course, these 47 patients were classified into CS type 1 ($n=41$; 21 surviving and 20 deceased), CS type 2 ($n=2$; both deceased), CS type 3 ($n=3$; all surviving), and CS+ XP type D (XP-D; $n=1$; deceased).

Incidence

To estimate the minimum number of CS patients in Japan, we divided the number of surviving patients (37) by the questionnaire response rate (73.2%). Thus, there were estimated to be approximately 50 CS patients in Japan. Using the Japanese population statistics for 2010, which state that the Japanese population is approximately 128 057 000 people, we calculated the prevalence of CS as 1 in 2 500 000.

Figure 1 shows the incidence of CS for every 5 year period from 1960 to 2009 according to the dates of birth of the 46 patients whose cases were examined in the secondary survey. According to the demographic trends outlined in the 2009 annual estimate of vital statistics published by the Ministry of Health, Labour, and Welfare (<http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei09/index.html>), approximately 37 540 000 neonates were born in Japan from 1980 to 2009. We calculated the incidence of CS per million births using the patient data for the period 1980–2009, given that before 1979 the methods used to diagnose CS might have been insufficient and some of the patient information for this period might have been lost. Assuming that between them the 921 hospitals diagnosed/treated all of the CS patients in Japan, and that the 30 CS patients not included in the secondary survey had the same incidence rate as the 40 CS patients from 1980 to 2009, we estimated the incidence of CS per million births using the following calculation: $76/37.54/0.732=2.77$. In

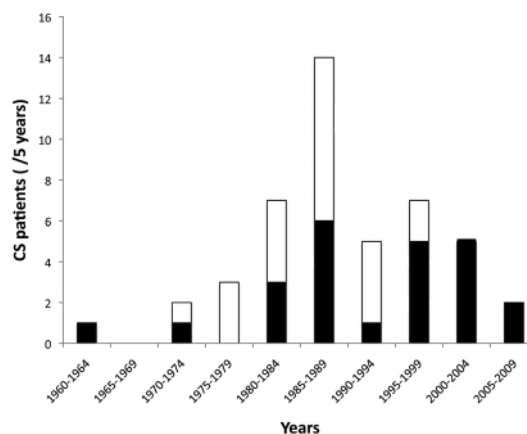


Fig. 1 Incidence of Cockayne syndrome (CS) from 1960 to 2009 in Japan. (□) Deceased; (■) surviving.

the calculation, 0.732 represents the response rate for the primary survey (95%CI: 2.19–3.11).

There were no significant regional differences in the distribution of CS throughout Japan. The patients were followed up by multiple specialists including child neurologists, orthopedic surgeons, rehabilitation specialists, ophthalmologists, otolaryngologists, dermatologists, dentists, and physiotherapists depending on their symptoms and needs.

CS type 1: surviving vs deceased patients

We compared the clinical data of the 21 surviving and 20 deceased CS type 1 patients and calculated the percentage of patients with various clinical manifestations and laboratory data for all 41 cases as shown in Table 1. The mean age of the surviving and the deceased patients were 16.1 and 18.9 years, respectively.

Mean age at time of diagnosis was 5 years. Concerning perinatal data, there was no significant difference in gestational age, frequency of asphyxia, or head circumference between the two groups. Although a small, but significant difference in birthweight was detected between the groups, its impact on subsequent clinical courses was unknown.

The frequencies of the following clinical symptoms and laboratory data differed significantly between the two groups: bodyweight and height stagnation, language delay, tube feeding, cause of death involving renal failure, proteinuria, anemia, sleep disorders, and lacrimal hyposecretion. In addition, elevated blood urea nitrogen (BUN) and creatinine (Cr) were significantly more prominent among the 20 deceased CS type 1 patients. One of the causes of death was severe renal failure in 9 of the 20 deceased CS type 1 cases. Mean age and bodyweight at death in the 20 deceased

Table 1 Symptoms and laboratory data of the 41 CS type 1 patients

	Surviving patients (n = 21)	Deceased patients (n = 20)	P	Total (n = 41) n (%)
Age (years) (range)/Sex	16.1 ± 8.6 (4–38)/14 M	18.9 ± 4.0 (14–27)/10 M	NS	
Gestational age (weeks)	39.4 (n = 20)	39.6 (n = 18)	NS	
Birthweight (g)	2776.8 (n = 20)	3065.2 (n = 18)	0.04	
Head circumference at birth (cm)	32.8 (n = 9)	32.4 (n = 4)		
Neonatal asphyxia	0 (n = 20)	3 (n = 19)	NS	3/39 (7.7)
Bodyweight (kg) (range)	15.3 (9–27) (n = 21)	12.6 (7–20) (n = 14)	0.04	
Height (cm) (range)	103.5 (85–125) (n = 20)	96.2 (87–103) (n = 10)	0.02	
Failure to thrive	20 (n = 20)	16 (n = 16)	NS	36/36 (100)
Able to walk	11 (n = 20)	10 (n = 18)	NS	21/38 (55.3)
Mean age started to walk (months)	25	19		
Able to speak	18 (n = 20)	12 (n = 19)	0.046	30/39 (76.9)
Mental retardation	21 (n = 21)	20 (n = 20)	NS	41/41 (100)
Oral nutrition	19 (n = 20)	6 (n = 17)	0.0001	25/37 (67.6)
Photosensitivity	17 (n = 19)	17 (n = 18)	NS	34/37 (91.9)
Sunken eyes	19 (n = 20)	19 (n = 19)	NS	38/39 (97.4)
Deafness	16 (n = 19)	12 (n = 12)	NS	28/31 (90.3)
Cataracts	11 (n = 17)	9 (n = 14)	NS	20/31 (64.5)
Retinopigmental changes	14 (n = 17)	11 (n = 11)	NS	25/28 (89.3)
Optic atrophy	6 (n = 14)	6 (n = 10)	NS	12/24 (50)
Scoliosis	9 (n = 19)	3 (n = 12)	NS	12/31 (38.7)
Foot joint contracture	18 (n = 19)	12 (n = 13)	NS	30/32 (93.4)
Decayed teeth	10 (n = 16)	8 (n = 9)	NS	18/25 (72)
Hypertension	3 (n = 10)	6 (n = 10)	NS	9/20 (45)
Renal failure	1 (n = 21)	9 (n = 13)	<0.001	10/34 (29.4)
Anemia	2 (n = 21)	8 (n = 15)	0.004	10/36 (27.8)
Lacrimal hyposecretion	2 (n = 12)	6 (n = 9)	0.02	8/21 (38.1)
Hypohydrosis	10 (n = 15)	8 (n = 10)	NS	18/25 (72)
Finger tremors	8 (n = 18)	9 (n = 12)	NS	17/30 (56.7)
Brisk DTR	12 (n = 19)	6 (n = 9)	NS	18/28 (64.3)
Seizures	4 (n = 20)	2 (n = 13)	NS	6/33 (18.2)
Sleep disorder	2 (n = 17)	5 (n = 11)	0.04	7/28 (25)
BT dysregulation	8 (n = 18)	4 (n = 7)	NS	12/25 (48)
Diarrhea	6 (n = 19)	5 (n = 9)	NS	11/28 (39.3)
Basal ganglia calcification	17 (n = 17)	11 (n = 12)	NS	28/29 (96.6)
Peripheral nerve conduction abnormalities	6 (n = 13)	3 (n = 6)	NS	9/19 (47.4)
Abnormal ABR	14 (n = 17)	4 (n = 4)		18/21 (85.7)
ALT (IU/dL)	63.9 (n = 20)	62.7 (n = 19)	NS	
AST (IU/dL)	114.8 (n = 20)	119.8 (n = 19)	NS	
BUN (mg/dL)	18.2 (n = 20)	40.5 (n = 17)	0.002	
Cr (mg/dL)	0.49 (n = 20)	1.67 (n = 16)	0.03	
Proteinuria	2 (n = 16)	9 (n = 11)	0.0003	11/28 (39.3)

(n), no. patients for whom data were available. ABR, auditory brainstem response; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BT, body temperature; BUN, blood urea nitrogen; Cr, creatinine; CS, Cockayne syndrome; DTR, deep tendon reflex; NS, not significant.

CS type 1 patients were 18.9 years and 12.6 kg, respectively. In contrast, only one of the 21 CS type 1 survivors (mean age, 16.1 years; mean bodyweight, 15.3 kg) had renal failure.

The following signs and symptoms were observed in >90% of the 41 CS type 1 patients: profound failure to thrive; photosensitivity; deafness; abnormal facial appearance (e.g. sunken eyes due to lack of subcutaneous orbital fat); foot joint contracture; intellectual disability; and basal ganglia calcification on computed tomography (CT; Table 1). In addition, abnormal auditory brainstem response, retinitis pigmentosa, and decayed teeth were also found in >70% of cases. Hypohydrosis, thermoregulation disorders, and hand tremor occurred in more than half of the patients. Although 20% of the patients had seizure disorders, they were easily controlled. Microcephaly was also a prominent finding. The mean head circumference of the 15 CS type 1 patients in whom this parameter was measured was 44.9 ± 1.8 cm. Miotic pupils and a high-pitched or husky voice were found in many patients, but no autistic tendencies were observed, and the patients' friendly and outgoing personalities remained unchanged despite the progression of the disease. These symptoms were also observed during the early stages of CS type 2 and the later stages of CS type 3, although severity varied markedly.

CS type 1 with severe renal failure

Recently, we encountered a patient with CS type 1, an 8-year-old girl (patient 1), who presented with severe renal failure (serum BUN, 40.8 mg/dL; serum Cr, 1.68 mg/dL; estimated glomerular filtration rate, 18.4 mL/min), stage 5 chronic kidney disease, anorexia, bodyweight loss (8.0 kg; SD, -3.7), and hypertension (systolic blood pressure, 140 mmHg). Renal biopsy led to the detection of global glomerulosclerosis, a tortuous and thickened basement membrane, the disappearance of podocytes, and renal tubular narrowing without mesangial proliferation (Fig. 2). After medical management of the patient's hypertension, anemia, hyperuricemia, acidosis, and heart failure, she underwent gastrostomy followed by catheter surgery to enable peritoneal dialysis. At 6 months after operation, her bodyweight had increased to 11.5 kg, and her daily activity levels had almost returned to their preoperative peak (Fig. 3). Before the patient suffered renal failure her oral food intake had reduced significantly, leading to cachexia. Such changes should be considered a warning sign.

CS type 2

Our nationwide survey included two patients with CS type 2 (patients 2,3). Both patients had a similar clinical course: that is, they had birthweight 2472 g and 2420 g, respectively, after being delivered at term without asphyxia, and they died of end-stage renal failure and pneumonia at 7 and 6 years of age, respectively, preceded by cachexic changes. At death, patients 2 and 3 weighed 4 kg and 7 kg, respectively. Both patients were fed with nasogastric tubes during the later stages. They were not able to speak any words and had mild photosensitivity, tremulous hand movements, foot joint contracture (equinovarus), and the typical facial appearance of CS before the age of 1. Patient 2's deafness (60–70 dB hearing loss) became apparent at 2 years of age and was temporarily improved with a hearing aid. Brain CT did not detect

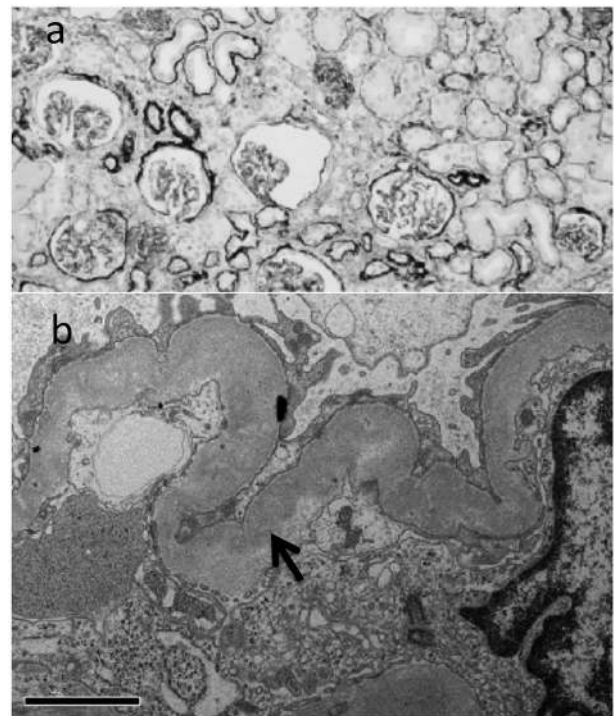


Fig. 2 Kidney biopsy findings of Cockayne syndrome type 1. (a) Small and collapsed glomeruli (global glomerulosclerosis) and narrowed tubules were observed. (b) A tortuous and thickened basement membrane and the disappearance of podocytes were also evident (arrow). Scale bar, 2 μ m.

calcification in patient 2, while magnetic resonance imaging (MRI) showed marked delayed myelination. Later, brain calcification developed and brain atrophy progressed rapidly (Fig. 4).

CS type 3 with neurogenic bladder

Of the three CS type 3 patients, two (twins) were simultaneously admitted to hospital at the age of 27 years because of post-renal failure urinary retention and abdominal distension. They had been healthy until their family noticed that they had unsteady gaits at the age of 17. We diagnosed them with CS type 3 based on clinical CS phenotype: late onset, skin UV sensitivity intermediate between that seen in patients with CS type 1 and that observed in normal controls; and the detection of basal ganglia calcification on CT at the age of 25 years (Fig. 5). A thick bladder wall, a distended bladder, bilateral hydronephrosis, and hydroureter were detected on ultrasound performed on admission. Supportive treatment including balloon-catheter installation, antibiotics, and hydration improved these symptoms. After this treatment their general condition remained stable, and they had normal renal function after the balloon-catheter installation, which was combined with regular bladder irrigation. Subsequently, however, their condition began to gradually worsen. In these patients, the neurogenic bladder might have been caused by peripheral neuropathy. Despite the fact that these patients were suffering from severe renal failure on admission, they recovered rapidly. This indicated that their renal function itself was not severely impaired. Unlike the CS type 1 patients, the glomerular function of the CS type 3 patients was considered to be almost normal. Compared with types 1 and 2, CS type 3

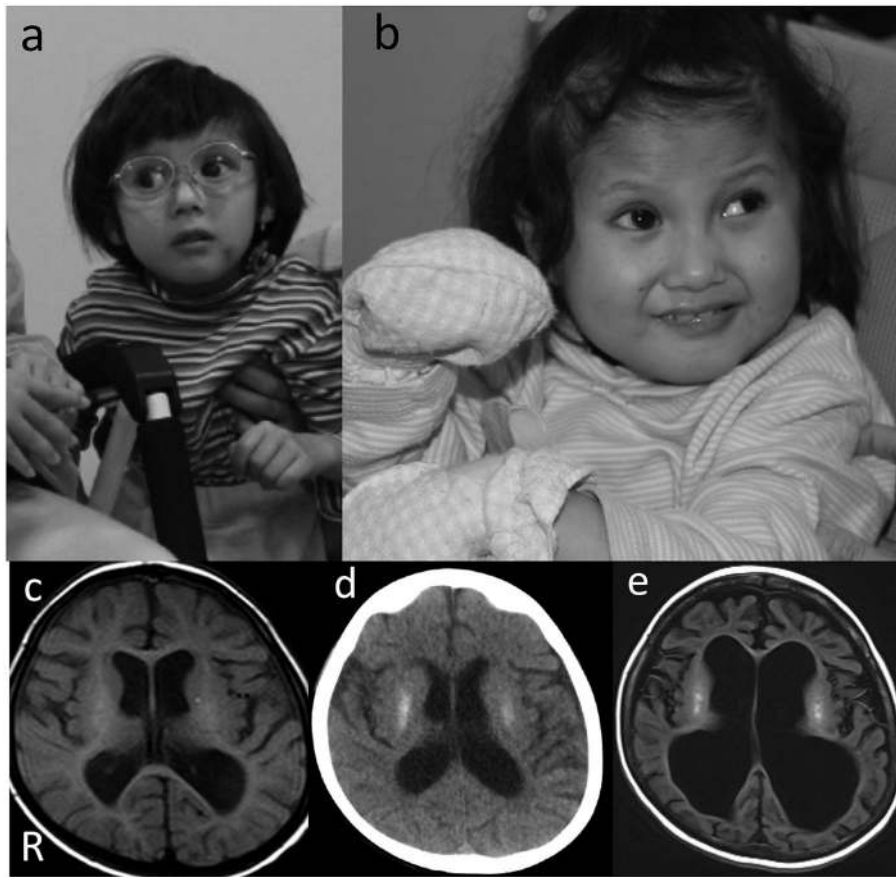


Fig. 3 Girl with Cockayne syndrome type 1 at (a) diagnosis (age, 5 years) and (b) after gastrostomy and initiation of peritoneal dialysis (age, 8 years). Improvement in nutritional status can be seen from her appearance. (c,e) Progression of cortical atrophy on brain magnetic resonance imaging (c, 5 years; e, 8 years). (d) Basal ganglia calcification was also noted on computed tomography at 5 years. (Reproduced with permission of the patient's family.)

involves late onset and a slow rate of symptom manifestation. In the aforementioned patients, marked gait difficulties did not develop until the subjects' late 20s, daily conversation was possible, and the typical facial appearance associated with CS was not obvious at first. In addition, the patients developed inconspicuous tooth decay, mild or negligible photosensitivity, and mild renal failure. The nosology and pathophysiology of the condition, however, are still poorly defined. Interestingly, on molecular genetic analysis of these two patients, no mutations were detected in the *ERCC6* (*CSB*), *ERCC8* (*CSA*), or *UVSSA* genes (Assoc. Professor T. Ogi, Nagasaki University, pers. comm., 2014).

CS classification based on motor development

Regarding motor development, especially in terms of locomotion ability, clear differences in the course of the disease exist among the three types of CS. In CS type 1, the subjects were initially able to walk alone (21/38, 55.3%; Table 1) or with assistance, but thereafter their condition gradually deteriorated. Conversely, the two CS type 2 patients could move only by crawling and could not stand up alone. As for the three CS type 3 patients, they had almost normal motor development and were usually able to walk by themselves until their late 20s, but their condition subsequently worsened slowly. In neurological examination of CS type 1, hyperreflexia

was observed in 18/28 patients (64.3%), the Babinski response was seen in 10/23 patients (43.5%), ankle clonus was noted in 7/24 patients (29.2%), and hypo- or areflexia was evident in 5/28 patients (17.9%). Peripheral nerve conduction analysis detected abnormalities in 9/19 patients (47.4%). The development of hyperreflexia or areflexia might depend upon the severity of pyramidal tract lesions, peripheral neuropathy, joint contracture, and/or muscle wasting. Multi-system degeneration including of the cortex, white matter, basal ganglia, cerebellum, and peripheral nervous system could be involved in the pathogenesis of the motor dysfunction seen in CS. In addition, the severity of such damage might affect the severity of motor dysfunction.

Cockayne syndrome involves marked and progressive locomotion disturbance, which is caused by a combination of spasticity, ataxia, peripheral neuropathy, and joint contracture. Calcification of the basal ganglia is common in CS, but involuntary movements such as dystonia are rare, except for finger tremors, which were seen in 17/30 patients (56.7%). Nance and Berry found that only four (3%) of 140 reviewed cases involved movement disorders.⁶ Rapin *et al.* reported that 9/21 adult patients had movement disorders (resting tremors in six cases and choreoathetosis in three cases).⁹ Deep brain stimulation or oral carbidopa–levodopa was reported to be clinically effective in some CS patients with movement

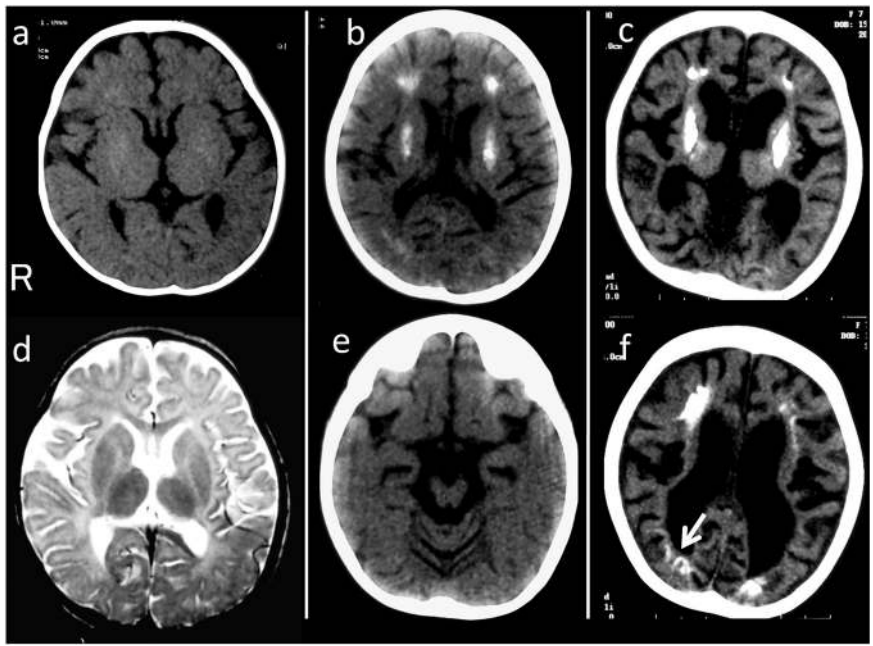


Fig. 4 Brain (a–c,e,f) computed tomography and (d) magnetic resonance imaging (MRI) in a patient with Cockayne syndrome type 2 at (a,d) 1 year; (b,e) 3 years 3 months; and (c,f) 7 years. (a) At the age of 1 year, no basal ganglia calcification was observed, while (d) hypomyelination was detected on T2-weighted MRI (high signal intensity in the posterior limb of the internal capsule). (b,e) Calcification subsequently developed in the basal ganglia and subcortical white matter, and (c,f) the brain atrophy progressed. (f) Calcification also appeared in the cortex at the depths of the sulci in the occipital region (arrow).

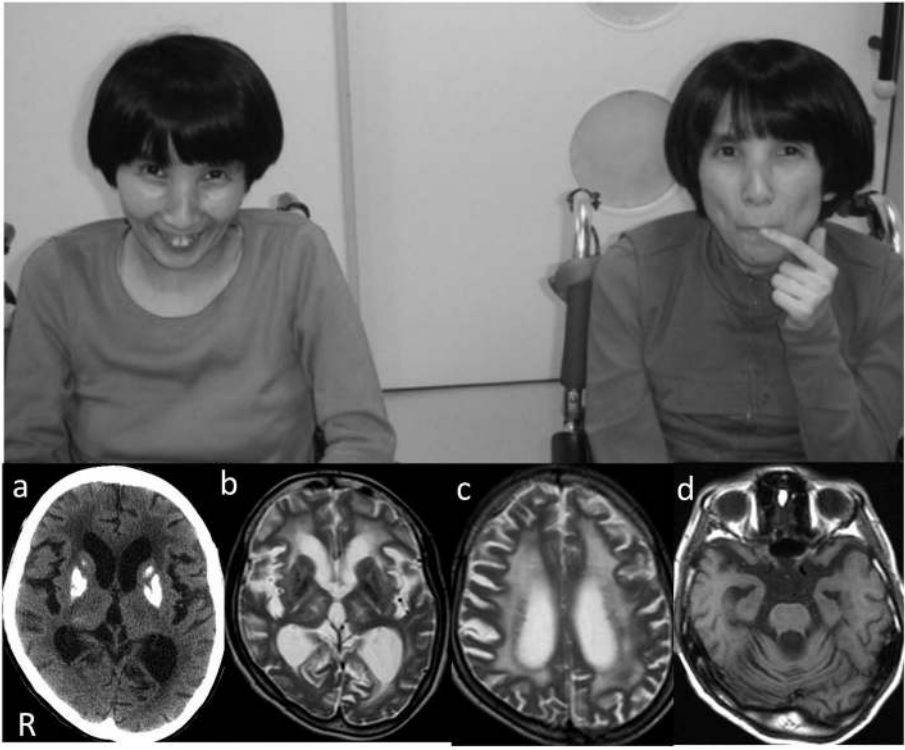


Fig. 5 Twins with Cockayne syndrome type 3. Brain (a) computed tomography and (b–d) magnetic resonance imaging (b,c, T2-weighted; d, T1-weighted) obtained at the age of 25. (a,b) Bilateral striatal calcification was evident. Cerebral and cerebellar atrophy, and abnormal signal changes in the white matter, striatum, and thalamus were found. (Reproduced with permission of the patients’ family.)

disorders (dystonia).^{10,11} We also noted improvement of hand tremor in CS type 3 patients after addition of an oral synthetic thyrotropin-releasing hormone analog, which has been widely used for treatment of spinocerebellar degeneration.

Neuroimaging

On CT, bilateral calcification of the basal ganglia, dentate nucleus, and subcortical white matter are diagnostic hallmarks of CS, but genetically confirmed CS without calcification has been reported in rare cases.^{12–14} Of the latter cases, those reported by Miyauchi *et al.* and Kennedy *et al.* corresponded to CS type 3.^{12,13} Brain calcification might not appear before the age of 1, even in CS type 2 (the severe form), as shown in Figure 4. Almost all CS type 1 and 3 patients, however, have brain calcification after the age of 3.¹⁴ Generally, there is no clear correlation between the extent of such calcification and age, the severity of neurological symptoms, or the degree of cerebral atrophy.¹⁴ In individual patients, however, brain atrophy and the progression of neurological symptoms are correlated to some extent (Fig. 4). On MRI, cerebral atrophy that predominantly involves white matter loss and regions of abnormal white matter signal intensity are the main features of CS. On CT, calcification appears as low-intensity regions on T2-weighted imaging (Fig. 5b) and as high-intensity regions on T1-weighted imaging (Fig. 3e). On occasion, hypointense foci are observed within the hyperintense white matter, which might correspond to tigroid leukodystrophy. On T2-weighted imaging, definitive myelination is absent from the supratentorial white matter from the first year of life in CS type 2 (Fig. 4d).¹⁴ In CS types 1 and 3, white matter loss takes a progressive course (Fig. 3c,e), which supports the involvement of dysmyelination and demyelination. The atrophy of the cerebellum and brainstem progresses slowly until the mid-stage of the course, but becomes much more evident later.

Neuropathology and oxidative stress

The main neuropathological features of CS are small cerebrum, tigroid leukoencephalopathy, basal ganglia calcification, cerebellar atrophy, advanced atherosclerosis, and a combination of demyelinating and axonal neuropathy without gross brain malformation.^{9,15} The neuropathology of CS indicates that it involves a mixture of developmental problems (e.g. dysmyelination), degeneration (e.g. demyelination), and premature aging affecting neurons, astrocytes, myelin sheaths, and blood vessels.¹⁶ Rapin *et al.* suggested that some of the white matter pathologies seen in CS might be related to microvascular pathologies because the better myelinated patches had preserved microvessels, whereas the demyelinated areas had increased numbers of string vessels (obliterated microvessels).⁹

Hayashi *et al.* reported that CS patients had increased numbers of small arteries and arterioles that were filled with fibrotic tissue, but free from arteriosclerosis, in the subarachnoid space and that small twisted and longitudinally running capillaries (string vessels as described by Rapin *et al.*)⁹ were observed in the cerebral white matter (Fig. 6).¹⁷ They speculated that oxidative stress might be involved in the generation of the vascular changes seen in the brain in CS due to the defective repair of oxidative DNA lesions. A reduction in DNA repair and the resultant DNA damage might be responsible for the excessive oxidative nucleotide damage seen in CS.¹⁵

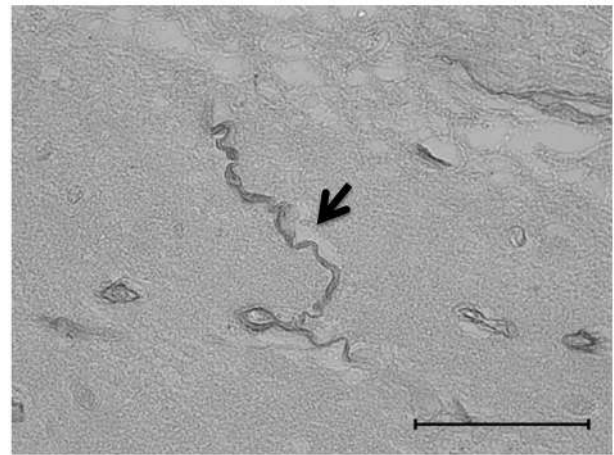


Fig. 6 Small twisted capillary (arrow) on immunostaining for collagen type IV in the cerebral white matter in Cockayne syndrome. Scale bar, 60 μ m.

As for the arteriosclerotic changes associated with CS, Rapin *et al.* and Mizuguchi and Itoh noted marked arteriosclerosis in CS type 3,^{9,16} while Hayashi *et al.* did not observe any arteriosclerosis in CS type 1 patients (aged 7–18 years) with string vessels.¹⁷ Although it is unclear whether these differences are age dependent, vascular changes in the brain might be involved in the neurological disturbances seen in CS.

In an investigation of autopsy cases, Hayashi examined oxidative stress in the brains of XP-A and CS patients.¹⁵ Lipid peroxidation and protein glycation markers were found in areas of perivascular calcification in the globus pallidus and cerebellum in both conditions, but such markers were more abundant in the CS patients than in the XP-A patients.

Unlike XP patients, CS patients are not at high risk of cancer; instead, they are considered to suffer from accelerated aging due to increased apoptosis. The increased apoptosis of CS cells might explain the lack of tumorigenesis in CS patients despite the increased rate of point mutations in their DNA.¹⁸

Care guidelines for CS

To date, no effective treatments have been developed for CS, and all current strategies focus on managing the symptoms of the condition.

We produced care guidelines for the daily management of CS based on how individual problems affect patients' daily lives, and these are available on our homepage (Cockayne Research and Care; <http://www.cockayneresearchcare.jp/>). These guidelines include information on how to deal with skin symptoms, decayed teeth, ophthalmological problems, movement disorders, renal failure, hypertension, epilepsy, nutrition, and sleep disorders. At present, the guidelines are available only in Japanese, but an English-language version is being prepared.

Discussion

Since the first description of CS by Cockayne in 1936,¹ more than 200 cases have been reported in the literature, but there have not

been many reports on the incidence of CS. This review included an analysis of 47 patients with clinically confirmed CS based on a nationwide survey conducted in Japan in 2009. It was limited by the lack of molecular diagnoses, although CS can be clinically diagnosed without difficulty. Nevertheless, the present data allowed us to estimate the incidence of CS in Japan and to compare findings with those of previous reports.

In the present study, we estimated that in Japan the incidence of CS is 2.77 per million births and the prevalence of CS is approximately 1 in 2 500 000. Kleijer *et al.* reported that the incidence of genetically confirmed CS (including XP/CS complex) in Western Europe is 2.7 per million births.⁸ These two estimates are similar, suggesting that any racial differences in the incidence of CS are not very large. There is a need for some caution regarding the present results. Most CS patients, even adults, are usually followed up by multiple specialists including child neurologists in Japan, but a few patients might not have been included in the present study because they were followed up only by adult neurologists. In addition, because of the difficulty in diagnosing CS early, we might have underestimated the number of patients for the period 2005–2009. Therefore, the present results should be regarded as minimum estimates.

Among the 41 CS type 1 patients, seven characteristics, that is, failure to thrive, photosensitivity, deafness, characteristic facial appearance of CS (sunken eyes), foot joint contracture, intellectual disability, and basal ganglia calcification on CT were observed in >90% of cases. These seven characteristics are important for early diagnosis and are included in the Sugarman *et al.* criteria.³ Of these, failure to thrive, photosensitivity, and intellectual disability (language delays) were seen before the age of 2 or 3. Deafness, typical facial appearance of CS, and basal ganglia calcification on CT became apparent later. As was found in previous reports, the clinical abnormalities associated with CS type 1 were not obvious in the perinatal period. Pediatricians play an important role in CS because it is typically diagnosable by the age of 3.

The mean age of the surviving and deceased CS type 1 patients was 16.1 and 18.9 years old, respectively. Most of the surviving patients were able to consume food orally, but the patients who died, had not been able to. Although the reduction in bodyweight associated with CS is not necessarily only a matter of nutrition, the initiation of tube feeding (via nasogastric tube or gastrostomy) might be necessary in the early stages of CS to delay cachexia. The present data suggest that good nutritional state facilitates a better prognosis. In fact, the two patients who underwent gastrostomy had good general condition (according to the survey), and their bodyweight increased after the operation. In addition to variation in nutritional status, differences in growth and language development were noted between the surviving and deceased CS type 1 patients. The role played by nutritional status in such developmental differences is unclear. Early and appropriate nutritional management might improve psychomotor development.

Given that the cause of death in CS patients is often associated with renal failure, renal function check-ups and the timely management of any problems are important. Nakajima *et al.* reported that in CS type 1, hyperuricemia appeared earlier, followed by serum Cr elevation and high blood pressure (before the age of 10).¹⁹

They emphasized that early evaluation of renal function is essential in CS involving patients of preschool age. Given that serum Cr tends to be underestimated in CS due to muscle wasting, cystatin C measurement is recommended during renal function check-up. Cystatin C is less dependent on age, sex, and muscle bulk than Cr. Motojima *et al.* showed that serum Cr corrected for height is very useful for evaluating renal function in CS patients ranging in age from 5 to 7.²⁰

Management is also important for hypertension and anemia derived from renal failure and poor nutrition. In cases of severe renal failure, peritoneal dialysis seems to be appropriate because hemodialysis and renal transplants are not feasible due to the small size of CS patients' blood vessels and their small physiques. Clinicians should be aware, however, of the limitations of peritoneal dialysis and potential complications such as peritonitis and degradation of the peritoneum. Although renal failure is not included in the diagnostic criteria for CS, it has an important influence on prognosis. Nance and Berry reported that renal complications develop in approximately 10% of CS patients.⁶ As shown in Table 1, out of 41 type 1 patients, 10/34 (29.4%) developed renal failure, 9/20 (45%) had hypertension, and 10/36 (27.8%) suffered anemia. In addition, the majority of the deceased patients (9/13, 69.2%) had suffered renal failure. Although the reason for the difference in the renal complication rate between the present study and the Nance and Berry study⁶ is unknown, appropriate follow up is necessary to avoid the systemic effects of renal failure in such cases.

Sleep disorders are uncommon in CS, but can represent a serious problem in daily life, and were more severe in the fatal cases (Table 1). Okoshi *et al.* suggested that selective acetylcholine neuron lesions in the pedunculopontine tegmental nucleus and/or the basal nucleus of Meynert and disturbed melatonin metabolism might be involved in the sleep disorders seen in CS.²¹ The melatonin agonist ramelteon and conventional hypnotics such as benzodiazepines might be effective against CS.

Nance and Berry examined 140 CS patients. Of these, 37 patients died, and their mean age at death was 12 years.⁶ It is unclear why the present patients had longer lifespans than those in the Nance and Berry study,⁶ but we consider that day-to-day care, including nutritional support, might be relevant.

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