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Medical Needs of Adults with Down Syndrome Presenting at a Regional Medical and Rehabilitation Center in Japan

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Background: Down syndrome (DS) is the most frequent chromosomal aberration; however, knowledge of associated health issues in adulthood is inadequate. We analyzed health data from Japanese adults with DS.

Methods: We conducted a retrospective chart review of 151 patients with DS who visited the Internal Medicine Outpatient Department of the Tokyo Metropolitan Kita Medical and Rehabilitation Center for the Disabled.

Results: Endocrine disorders such as obesity, hyperlipidemia, and hyperuricemia were most common in adulthood (≤40 years) and senescence (>40 years); neurological diseases were more prevalent in senescence. Multimorbidity was noted even patients with DS who were younger than 30 years, and the prevalence increased with age. Only 21 patients (13.9%) with DS visited our hospital with referral letters from pediatricians; 94 patients (62.3%) visited without such referrals from other medical institutions. Patients without a referral letter had a mean of 3.1 comorbidities per patient. Moreover, medical care for some people with DS was interrupted during childhood.

Conclusions: Prevention and detection of comorbidities in patients with DS requires continuous medical care from childhood through adulthood. Recently, DS has been diagnosed by chromosome testing and genetic counseling. Clinical geneticists and genetic counselors can help patients with DS, and their caregivers, to obtain appropriate health care and achieve well-being on their own by seamlessly engaging them throughout childhood and adulthood. (J Nippon Med Sch 2023; 90: 210–219)

Key words: down syndrome, obesity, hyperuricemia, multimorbidity, health services for persons with disabilities

Introduction

Down syndrome (DS) is the most frequent chromosomal aberration and is associated with varying severity of intellectual disability and comorbidities[1]. The average life expectancy of people with DS is over 60 years[2–4]. In Japan, the number of live births of children with DS was estimated to be 1 in 500, a higher rate than in Western countries, owing to advanced maternal age[5]. In addition, among Japanese with DS, the proportion of those older than 60 years is increasing, and the oldest person with DS in Japan was reported to be 102 years of age[6]. Therefore, lifelong continuous support for people with DS is essential because of their longer lifespans. Knowledge of comorbidities and the need for health supervision of chil-

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https://doi.org/10.1272/jnms.JNMS.2023_90-211
Journal Website (https://www.nms.ac.jp/sh/jnms/)

dren with DS has accumulated over decades, and health supervision of children with DS is already established and widely available in clinical practice[1,7]. However, the medical needs of adults with DS have been neglected[8]. Only a few observational studies have evaluated common comorbidities in adults with DS and offered recommendations for further surveillance[8–15]. Furthermore, only one study reported the prevalences of comorbidities for Japanese adults with DS living in residential facilities[16]. Thus, the medical needs of Japanese adults with DS are not fully understood. To assess the medical needs of adults with DS, we conducted a retrospective chart review of patients with DS who presented at the internal medicine outpatient department of our hospital.

Methods

Participants

We analyzed data from Japanese patients with DS who first visited the Internal Medicine Outpatient Department of Tokyo Metropolitan Kita Medical and Rehabilitation Center for the Disabled between January 1, 1988, and July 31, 2018. We mailed the study descriptions and informed consent documents to the patients and their caregivers. The patients were able to refuse access to their medical records by phone or e-mail. Consent was assumed to be given when patients did not refuse access.

Data Collection and Measures

We reviewed the medical charts of the patients and collected data on (1) gender, age at first visit, birth year, living conditions, daytime activities, karyotype, intelligence quotient (IQ), past medical history of congenital heart disease, thyroid dysfunction, leukemia, and cervical spine disease; (2) height, weight, and calculated body mass index (BMI); and (3) the purpose of the first visit. In accordance with the obesity criteria of the Japan Society for the Study of Obesity, obesity was diagnosed when BMI exceeded 25[17,18].

We performed a retrospective chart review to identify the health problems and comorbidities of patients with DS from the first visit to 6 months later. All health problems of patients with DS were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and comorbidities were defined according to ICD-10 codes Ver. 2019[19]. Chronic conditions diagnosed before visiting the internal medicine outpatient department were defined as comorbidities. We excluded intellectual disabilities from comorbidities because all people with DS have such disabilities[1,7,14]. Using Bittles' 4 ages of DS-the prenatal period, childhood/early adulthood, adulthood, and senescence[9]-we divided patients into 2 age groups: adulthood (age ≤40 years) and senescence (age >40 years), and disease prevalence was compared between the 2 groups.

We also ascertained the presence and source of referral letters from other medical centers, compared differences in disease prevalence between patients with a referral letter from a pediatrician or non-pediatrician, and noted the characteristics of comorbidities of patients without referral letters.

Data Analysis

The collected data were analyzed using Microsoft Excel for Mac version 16.51, are presented as mean ± SD, and were tabulated with JMP 14.2.0 software (SAS Institute, Cary, NC, USA). Descriptive statistics were used to analyze patient characteristics and prevalence rates.

Ethical Considerations

This study was approved by the Ethics Board of the Tokyo Metropolitan Kita Medical and Rehabilitation Center for the Disabled (August 8, 2018, Reception No. 149).

Results

Characteristics of Patients

We asked 155 patients with DS to participate in the study: 4 declined and 151 agreed to participate. The age, birth year, living conditions, daytime activities, karyotype, and BMI of the patients are shown in **Table 1**. The youngest patient was 14 years of age, and there were 29 teenagers (age 14-19 years); the Department of Internal Medicine of Kita Medical and Rehabilitation Center for the Disabled did not restrict their age. Sixty-three patients underwent chromosome testing in childhood (**Table 1**); however, approximately 60% of the sample had unknown chromosome test results.

All patients were clinically diagnosed as having intellectual disabilities and required assistance in daily life. The Tanaka-Binet Intelligence Scale was used to evaluate the IQ of 31 patients; however, 4 of these patients could not complete the test because of severe intellectual disabilities. The mean ± SD IQ of the other 27 patients was 23.3 ± 8.4, and there was no difference between sexes. Regarding past medical history, 46 patients (30.5% of the total) had congenital heart disease, 10 (6.6%) had thyroid disease, 9 (6.0%) had cervical spine disease, and 1 (0.7%) had acute lymphoblastic leukemia. Of the 10 patients with thyroid disease, 6 had hypothyroidism, 3 had Basedow's disease, and 1 had both hyper- and hypothyroidism. Among the 9 patients with cervical spine disease, 6

Table 1 Characteristics of patients with Down syndrome

	Overall (N = 151)	Male (n = 85)	Female (n = 66)
Age at first visit, years, mean ± SD (range)	30.3 ± 11.5 (14-64)	29.4 ± 10.8 (14-58)	31.4 ± 12.4 (15-64)
Range of birth years, calendar year	1939-2002	1941-2000	1939-2002
Living conditions, n (%)			
Home	132 (87.4)	77 (90.6)	55 (83.3)
Residential facility	19 (12.6)	8 (9.4)	11 (16.7)
Daytime activities, n (%)			
Regular employment	10 (6.6)	9 (10.6)	1 (1.5)
Employment for persons with disabilities	59 (39.1)	32 (37.6)	27 (41.0)
Daycare	34 (22.5)	20 (23.5)	14 (21.2)
Student	14 (9.3)	6 (7.1)	8 (12.1)
No activity	13 (8.6)	5 (5.9)	8 (12.1)
Unknown	21 (13.9)	13 (15.3)	8 (12.1)
Karyotype, n (%)			
Trisomy 21	61 (40.5)	33 (38.8)	28 (42.4)
Mosaicism	1 (0.7)	0 (0.0)	1 (1.5)
Robertsonian translocation*	1 (0.7)	1 (1.2)	0 (0.0)
Unknown	88 (58.1)	51 (60.0)	37 (56.1)
Body mass index (BMI), kg/m^2, mean ± SD	25.1 ± 6.4 (n = 116)	25.4 ± 6.7 (n = 66)	24.8 ± 5.9 (n = 50)
BMI classification, n (%)†			
Underweight: below 18.4	11 (9.5)	6 (9.1)	5 (10.0)
Normal weight: 18.5-24.9	51 (44.0)	32 (48.5)	19 (38.0)
Obesity: 25.0 or higher	54 (46.5)	28 (42.4)	26 (52.0)

SD, standard deviation

* Robertson translocation occurred only once, rob (14; 21)

† Percentage of the number of people for whom BMI was calculated

had congenital anomalies of the cervical spine, 2 had cervical spondylosis, and one had spondylolisthesis.

The purpose of the first visit was examination and treatment, for 99 patients (65.5%), a health checkup, for 43 patients (28.5%), and assessment of an abnormality discovered during a health checkup, for 9 patients (6.0%).

Comorbidities

Figure 1 shows the prevalence of all health problems, as defined in the ICD-10, among patients with DS in adulthood (≤40 years) and senescence (>40 years). **Table 2** shows the original data, ICD-10 chapter, and simple names. In Chapter IV, endocrine, nutritional, and metabolic diseases (described as "endocrine" in **Fig. 1**) were the most frequent during adulthood and senescence, although prevalence was higher in adulthood (71.4%) than in senescence (62.5%). Among adults with endocrine disorders, >30% had obesity, hyperlipidemia, and hyperuricemia, and approximately 20% had thyroid disease. Regarding senescence, 25% of patients had obesity, hyperlipidemia, and hyperuricemia, and 15% had thyroid disease. Chapter XVII diseases (congenital malformations, deformations, and chromosomal abnormalities [congenital]), Chapter XI diseases (diseases of the digestive system [digestive]), Chapter XII diseases (diseases of the skin and subcutaneous tissue [skin]), and Chapter I diseases (certain infectious and parasitic diseases [infection]) were more frequent in adulthood than in senescence. Congenital disorders include congenital heart disease and congenital anomalies of the cervical spine in the ICD-10 classification and increased in frequency in adulthood. Digestive disorders were the third most common health problem among patients: 25.8% had fatty liver, classified as other diseases of the liver. The prevalence of Chapter VI disorders-diseases of the nervous system (neurological)-was higher in senescence (50.0%) than in adulthood (6.7%). This increase resulted from the higher incidences of Alzheimer's disease (34.4%) and epilepsy (31.3%) in senescence, and all patients older than 51 years of age had neurological diseases. Furthermore, during senescence, patients had more disorders of the eyes and circulation, musculoskeletal disorders, and mental health disorders than did those in adulthood.

The average number of comorbidities defined in the ICD-10 chapters increased from 2.1 at age 14-20 years to 3.0 at age 51-64 years (**Fig. 2**). Seven patients had no medical history of comorbidities.

Patients with DS with and without Referral Letters

Among 57 patients (37.7%) with referral letters, 21

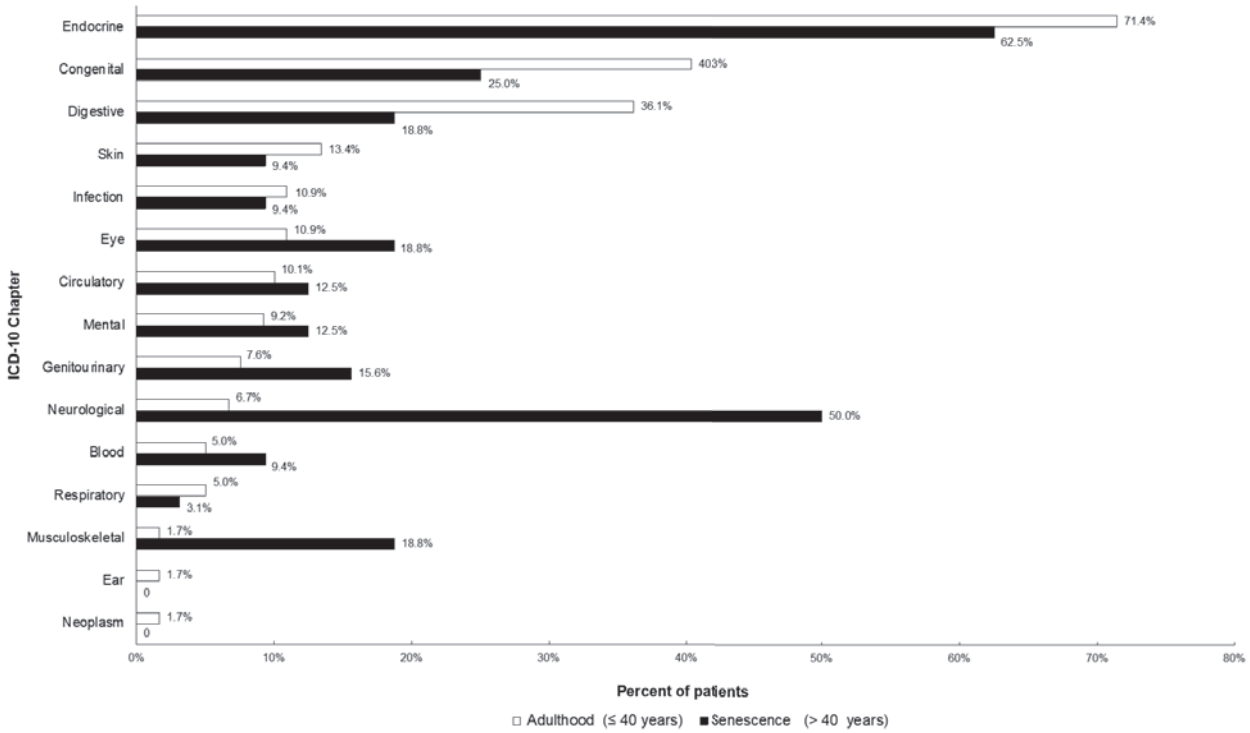

Fig. 1 Prevalence of comorbidities, as defined in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), in patients with Down syndrome.
Patients were counted as one if they had at least one disease in an ICD-10 chapter (simple names are used in Fig. 1) and were classified as adult (≤40 years) (n = 119) and senescent (>40 years) (n = 32)[9]. Table 2 shows the original data. Patient comorbidities are listed in descending order of prevalence in adulthood. Because most patients had more than one comorbidity, the number of people with health problems classified by chapter in the ICD-10 is less than the total number of disease codes.

(13.9%) and 36 (23.8%) had referrals from pediatricians and non-pediatric practitioners, respectively. Of the 57 patients with referral letters, each patient had between 1 and 7 (mean ± SD: 3.5 ± 1.6) comorbidities. Endocrine disorders were the most common comorbidity in 47 patients, followed by digestive and congenital disorders in 21 patients and neurological and eye disorders in 10 patients. Of those with referrals from pediatricians or non-pediatricians, the number of disorders diagnosed was 3.4 ± 1.8 and 3.5 ± 1.5, respectively. Both patient groups had a high prevalence of endocrine disorders.

Ninety-four patients (62.3%) visited without a referral letter from other medical institutions, and 87 of them had between 1 and 7 (mean ± SD: 3.1 ± 1.8) comorbidities per patient. Endocrine disorders were the most frequent comorbidity in 58 patients, followed by congenital; digestive; neurological; circulatory and skin; and infection and mental health disorders-35, 28, 14, 12, and 11 patients, respectively. There was no difference between adulthood and senescence in the proportion of patients without referral letters: 72 (60.5%) of 119 patients in adulthood and 22 (68.8%) of 32 patients in senescence did not have such letters.

Genetic Counseling and Medical Follow-Up

A genetic specialist and counselor performed genetic counseling and chromosomal tests for 13 patients. During genetic counseling, the purpose and implications of the test were explained, and information on the genetic basis of DS was shared. We provided all patients with general medical information on adults with DS, such as comorbidities and natural history, to support them in adapting to their condition. We regularly monitored the health status of all DS patients.

Discussion

This study analyzed data from patients with DS aged 14-64 years who visited an internal medicine outpatient department. Adults with DS had many comorbidities in their teens and twenties, and the number of comorbidities increased with age. The present results show a high prevalence of endocrine disorders in adult and senescent patients with DS. Endocrine disorders include obesity, hyperlipidemia, hyperuricemia, and thyroid disease. Studies of adults with DS[8–14,20,21] reported that obesity, hy-

Table 2 ICD-10 coding for defining comorbidities in patients with Down syndrome

Chapter/Disease code (abbreviation)	Cumulative total number of patients with each chapter/ disease code					
	≤40 years (n = 119)		>40 years (n = 32)		Overall (n = 151)	
	Number	Percent	Number	Percent	Number	Percent
IV Endocrine, nutritional and metabolic diseases (Endocrine)	85	71.4%	20	62.5%	105	69.5%
Obesity	50	42.0%	8	25.0%	58	38.4%
Disorders of purine and pyrimidine metabolism	48	40.3%	9	28.1%	57	37.7%
Disorders of lipoprotein metabolism and other lipidaemias	32	26.9%	9	28.1%	41	27.2%
Other hypothyroidism	17	14.3%	2	6.3%	19	12.6%
Diabetes mellitus	7	5.9%	3	9.4%	10	6.6%
Thyrotoxicosis [hyperthyroidism]	6	5.0%	0	0.0%	6	4.0%
Thyroiditis	1	0.8%	2	6.3%	3	2.0%
Other disorders of fluid, electrolyte and acid-base balance	1	0.8%	1	3.1%	2	1.3%
Hypofunction and other disorders of pituitary gland	1	0.8%	0	0.0%	1	0.7%
Volume depletion	0	0.0%	1	3.1%	1	0.7%
XVII Congenital malformations, deformations and chromosomal abnormalities (Congenital)	48	40.3%	8	25.0%	56	37.1%
Congenital malformations of cardiac septa	32	26.9%	4	12.5%	36	23.8%
Congenital malformations of great arteries	9	7.6%	0	0.0%	9	6.0%
Congenital musculoskeletal deformities of head, face, spine and chest	8	6.7%	5	15.6%	13	8.6%
Other congenital malformations of heart	3	2.5%	0	0.0%	3	2.0%
XI Diseases of the digestive system (Digestive)	43	36.1%	6	18.8%	49	32.5%
Other diseases of liver	34	28.6%	5	15.6%	39	25.8%
Other functional intestinal disorders	5	4.2%	1	3.1%	6	4.0%
Haemorrhoids and perianal venous thrombosis	3	2.5%	0	0.0%	3	2.0%
Gastro-oesophageal reflux disease	2	1.7%	0	0.0%	2	1.3%
Gingivitis and periodontal diseases	1	0.8%	0	0.0%	1	0.7%
Gastric ulcer	1	0.8%	0	0.0%	1	0.7%
Inguinal hernia	1	0.8%	0	0.0%	1	0.7%
Diaphragmatic hernia	1	0.8%	0	0.0%	1	0.7%
Other diseases of digestive system	1	0.8%	0	0.0%	1	0.7%
Cholelithiasis	0	0.0%	1	3.1%	1	0.7%
XII Diseases of the skin and subcutaneous tissue (Skin)	16	13.4%	3	9.4%	19	12.6%
Cicatricial alopecia [scarring hair loss]	4	3.4%	0	0.0%	4	2.6%
Atopic dermatitis	2	1.7%	0	0.0%	2	1.3%
Other dermatitis	2	1.7%	2	6.3%	4	2.6%
Corns and callosities	2	1.7%	0	0.0%	2	1.3%
Psoriasis	2	1.7%	0	0.0%	2	1.3%
Dermatitis due to substances taken internally	1	0.8%	0	0.0%	1	0.7%
Follicular cysts of skin and subcutaneous tissue	1	0.8%	0	0.0%	1	0.7%
Nail disorders	1	0.8%	0	0.0%	1	0.7%
Decubitus ulcer and pressure area	1	0.8%	1	3.1%	2	1.3%
Unspecified contact dermatitis	1	0.8%	0	0.0%	1	0.7%
Acanthosis nigricans	1	0.8%	0	0.0%	1	0.7%
Vitiligo	0	0.0%	1	3.1%	1	0.7%
I Certain infectious and parasitic diseases (Infection)	13	10.9%	3	9.4%	16	10.6%
Dermatophytosis	6	5.0%	2	6.3%	8	5.3%
Other gastroenteritis and colitis of infectious and unspecified origin	6	5.0%	1	3.1%	7	4.6%
Chronic viral hepatitis	1	0.8%	0	0.0%	1	0.7%
VII Diseases of the eye and adnexa (Eye)	13	10.9%	6	18.8%	19	12.6%
Other cataract	9	7.6%	6	18.8%	15	9.9%

Table 2 ICD-10 coding for defining comorbidities in patients with Down syndrome (continued)

Chapter/Disease code (abbreviation)	Cumulative total number of patients with each chapter/ disease code					
	≤40 years (n = 119)		>40 years (n = 32)		Overall (n = 151)	
	Number	Percent	Number	Percent	Number	Percent
Disorders of refraction and accommodation	3	2.5%	0	0.0%	3	2.0%
Other disorders of eyelid	2	1.7%	0	0.0%	2	1.3%
Conjunctivitis	1	0.8%	0	0.0%	1	0.7%
Visual disturbances	1	0.8%	0	0.0%	1	0.7%
IX Diseases of the circulatory system (Circulatory)	12	10.1%	4	12.5%	16	10.6%
Cerebral infarction	3	2.5%	2	6.3%	5	3.3%
Nonrheumatic mitral valve disorders	2	1.7%	0	0.0%	2	1.3%
Other conduction disorders	2	1.7%	0	0.0%	2	1.3%
Nonrheumatic aortic valve disorders	1	0.8%	1	3.1%	2	1.3%
Other diseases of pericardium	1	0.8%	0	0.0%	1	0.7%
Atrioventricular and left bundle-branch block	1	0.8%	0	0.0%	1	0.7%
Other cardiac arrhythmias	1	0.8%	0	0.0%	1	0.7%
Heart failure	1	0.8%	0	0.0%	1	0.7%
Other cerebrovascular diseases	1	0.8%	0	0.0%	1	0.7%
Pulmonary embolism	0	0.0%	1	3.1%	1	0.7%
Complications and ill-defined descriptions of heart disease	1	0.8%	0	0.0%	1	0.7%
V Mental and behavioural disorders (Mental)	11	9.2%	4	12.5%	15	9.9%
Depressive episode	3	2.5%	0	0.0%	3	2.0%
Unspecified dementia	2	1.7%	2	6.3%	4	2.6%
Obsessive-compulsive disorder	2	1.7%	0	0.0%	2	1.3%
Persistent delusional disorders	1	0.8%	1	3.1%	2	1.3%
Other disorders of adult personality and behaviour	1	0.8%	1	3.1%	2	1.3%
Schizoaffective disorders	1	0.8%	0	0.0%	1	0.7%
Pervasive developmental disorders	1	0.8%	0	0.0%	1	0.7%
Tic disorders	1	0.8%	0	0.0%	1	0.7%
XIV Diseases of the genitourinary system (Genitourinary)	9	7.6%	5	15.6%	14	9.3%
Excessive, frequent and irregular menstruation	3	2.5%	0	0.0%	3	2.0%
Neuromuscular dysfunction of bladder, not elsewhere classified	2	1.7%	3	9.4%	5	3.3%
Cystitis	2	1.7%	0	0.0%	2	1.3%
Other disorders of urinary system	1	0.8%	2	6.3%	3	2.0%
Other disorders of kidney and ureter, not elsewhere classified	1	0.8%	1	3.1%	2	1.3%
VI Diseases of the nervous system (Neurological)	8	6.7%	16	50.0%	24	15.9%
Epilepsy	5	4.2%	10	31.3%	15	9.9%
Sleep disorders	3	2.5%	0	0.0%	3	2.0%
Other disorders of brain	1	0.8%	0	0.0%	1	0.7%
Alzheimer disease	0	0.0%	11	34.4%	11	7.3%
Parkinson disease	0	0.0%	1	3.1%	1	0.7%
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (Blood)	6	5.0%	3	9.4%	9	6.0%
Other anaemias	5	4.2%	3	9.4%	8	5.3%
Other diseases of blood and blood-forming organs	1	0.8%	0	0.0%	1	0.7%
X Diseases of the respiratory system (Respiratory)	6	5.0%	1	3.1%	7	4.6%
Acute upper respiratory infections of multiple and unspecified sites	2	1.7%	0	0.0%	2	1.3%
Acute tonsillitis	1	0.8%	0	0.0%	1	0.7%
Influenza due to identified seasonal influenza virus	1	0.8%	0	0.0%	1	0.7%
Bronchitis, not specified as acute or chronic	1	0.8%	0	0.0%	1	0.7%

Table 2 ICD-10 coding for defining comorbidities in patients with Down syndrome (continued)

Chapter/Disease code (abbreviation)	Cumulative total number of patients with each chapter/ disease code					
	≤40 years (n = 119)		>40 years (n = 32)		Overall (n = 151)	
	Number	Percent	Number	Percent	Number	Percent
Simple and mucopurulent chronic bronchitis	1	0.8%	0	0.0%	1	0.7%
Asthma	1	0.8%	0	0.0%	1	0.7%
Abscess of lung and mediastinum	0	0.0%	1	3.1%	1	0.7%
XIII Diseases of the musculoskeletal system and connective tissue (Musculoskeletal)	2	1.7%	6	18.8%	8	5.3%
Spondylosis	1	0.8%	2	6.3%	3	2.0%
Acquired deformities of fingers and toes	1	0.8%	0	0.0%	1	0.7%
Osteoporosis without pathological fracture	0	0.0%	1	3.1%	1	0.7%
Other spondylopathies	0	0.0%	3	9.4%	3	2.0%
Other deforming dorsopathies	0	0.0%	1	3.1%	1	0.7%
VIII Diseases of the ear and mastoid process (Ear)	2	1.7%	0	0	2	1.3%
Other hearing loss	2	1.7%	0	0.0%	2	1.3%
II Neoplasms (Neoplasm)	2	1.7%	0	0	2	1.3%
Benign lipomatous neoplasm	1	0.8%	0	0.0%	1	0.7%
Lymphoid leukaemia	1	0.8%	0	0.0%	1	0.7%

ICD-10 International Statistical Classification of Diseases and Related Health Problems 10th Revision [World Health Organization. ICD-10 Ver.2019]

Because some patients have more than one complication, the number of people with complications classified by chapter in ICD-10 is less than the total number of disease codes.

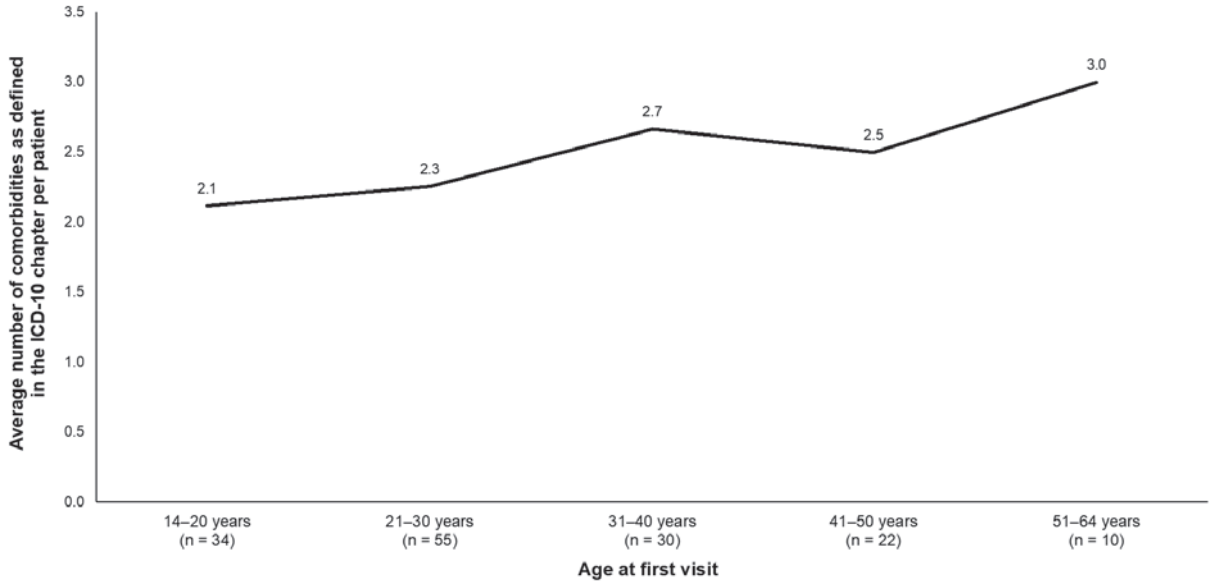

Fig. 2 Average number of comorbidities per patient with Down syndrome, by age group.
Comorbidities were defined in relation to the corresponding chapter in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Even patients aged 14-20 years exhibited multimorbidity.

perlipidemia, and thyroid disease were comorbidities. In addition, clinical guidelines for adults with DS recommend screening for obesity and diabetes mellitus[22]. However, these studies were conducted at centers outside Japan. Because the prevalence of obesity varies by population[2,10,23], it is difficult to compare the present results with those from studies of non-Japanese patients. Furthermore, there were no reports of hyperuricemia in previous studies[8–14,20,21,23,24] or clinical guidelines for adults with DS[22]. The first mention of hyperuricemia in patients with DS was in the early 1960s[25]. Ueda *et al*.[16] reported that adults with DS had hyperlipidemia, hypothyroidism, and hy-

peruricemia. The authors focused on obesity-related health disorders and highlighted the importance of comprehensive health management from childhood through adulthood. In their report, the number of obese patients was small (5 of 36 males, 4 of 23 females) because the participants lived regularly and received periodic health checkups and guidance from a residential facility; therefore, the authors emphasized the need for further research. The present study analyzed data from non-institutionalized outpatients and found comorbidities similar to those described by Ueda and colleagues. Our results suggest that adults with DS have variable comorbidities, especially obesity, hyperlipidemia, hyperuricemia, and thyroid disease. It is unclear whether DS increases the risk of hyperuricemia, and Japanese studies have found no consistent association between obesity and uric acid level in DS[16,26]. Hypotheses to explain hyperuricemia in DS include increased dietary purines[27], the effects of sex hormones, the growth and aging process[28], and alterations in oxidative stress pathways[29,30]. However, the relationship between hyperuricemia and DS requires further investigation.

Comorbidities differed between adulthood and senescence (**Fig. 1**). In particular, neurological diseases were more prevalent during senescence, and all patients with Alzheimer's disease were senescent. In adults with DS, the incidence of cognitive decline is high in adults older than 40 years[31], the prevalence of dementia increases sharply, and seizure disorders are significantly more frequent with advancing age[13,15,32]. Therefore, those caring for adults with DS must consider neurological disease as a comorbidity in senescence.

In the present study, only 21 patients (13.9%) with DS visited our outpatient department with referral letters from pediatricians, and 94 (62.3%) patients visited our outpatient department without such letters from other medical centers. Patients without a referral letter had a mean of 3.1 comorbidities per patient. We did not ascertain why patients with DS presented at our hospital without a referral letter. A possible reason is that children with DS often complete treatment for medical complications in infancy or early childhood, and their susceptibility to infectious diseases stabilizes after they start school. Hence, medical care for patients with DS is often interrupted during childhood, leading to comorbidities. Long-term follow-up is recommended for patients with DS, to ensure early detection of comorbidities. The transition from pediatric to adult healthcare for individuals with childhood-onset neurological conditions, including DS, requires multidisciplinary involvement. The transition to adult healthcare supports individuals in optimizing medical treatment and improving the health awareness of patients and families[33]. Some comorbidities can be prevented if patients receive appropriate medical care. Clinicians need to be aware of the unique health problems of adults with DS and to establish a pattern of regular health checkups[8,10,22]. Therefore, addressing prevention and early detection of comorbidities in patients with DS from childhood through adulthood is necessary. Because intellectual disability may make it difficult for patients with DS to describe their condition, health checkups are one of the many reasons for visits to our hospital. The people around them need to be aware of the condition of patients with DS. Recently, DS has been diagnosed using chromosome testing and genetic counseling[3,34–36]. Past and present studies of comorbidities in adults with DS indicate the critical importance of providing information on appropriate health management protocols. Clinical geneticists and genetic counselors can support patients with DS and their caregivers to achieve proper healthcare and well-being on their own by seamlessly engaging them throughout childhood and adulthood.

Conclusion

Adults with DS have a variety of comorbidities, and a unique characteristic of adults with DS is the presence of multiple comorbidities. Moreover, many people with DS have intellectual disabilities and thus require assistance in their lives. Genetic counseling can support people with DS from childhood through adulthood and engage patients and their families in obtaining appropriate medical care.

Limitations of This Study and Future Prospects

This study is limited by the generalizability of the results. Although our center is located in a secondary medical area with a population of approximately 1.92 million people, and patients from other prefectures and regions also visit, a survey of a single center cannot reflect the entire cohort of Japanese adults with DS. A second limitation is that some data were missing in medical records; nonetheless, our 30-year record of medical data is comprehensive and largely complete.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Bull MJ. Down syndrome. N Engl J Med. 2020 Jun;382 (24):2344–52.

2. Presson AP, Partyka G, Jensen KM, et al. Current estimate of Down syndrome population prevalence in the United States. J Pediatr. 2013 Oct;163(4):1163−8.
3. Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH. The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clin Genet. 2002 Nov;62(5):390−3.
4. Bittles AH, Glasson EJ. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. Dev Med Child Neurol. 2004 Apr;46(4):282−6.
5. Sasaki A, Sago H. Equipoise of recent estimated Down syndrome live births in Japan. Am J Med Genet A. 2019 Sep;179(9):1815−9.
6. Motegi N, Morisaki N, Suto M, Tamai H, Mori R, Nakayama T. Secular trends in longevity among people with Down syndrome in Japan, 1995-2016. Pediatr Int. 2021 Jan;63(1):94−101.
7. Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics. 2011 Aug;128 (2):393−406.
8. Henderson A, Lynch SA, Wilkinson S, Hunter M. Adults with Down's syndrome: the prevalence of complications and health care in the community. Br J Gen Pract. 2007 Jan;57(534):50−5.
9. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. Eur J Public Health. 2007 Apr;17 (2):221−5.
10. Capone GT, Chicoine B, Bulova P, et al. Co-occurring medical conditions in adults with Down syndrome: a systematic review toward the development of health care guidelines. Am J Med Genet A. 2018 Jan;176(1):116−33.
11. van Allen MI, Fung J, Jurenka SB. Health care concerns and guidelines for adults with Down syndrome. Am J Med Genet. 1999 Jun;89(2):100−10.
12. Alexander M, Petri H, Ding Y, Wandel C, Khwaja O, Foskett N. Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. Dev Med Child Neurol. 2016 Mar;58(3):246−54.
13. Glasson EJ, Dye DE, Bittles AH. The triple challenges associated with age-related comorbidities in Down syndrome. J Intellect Disabil Res. 2014 Apr;58(4):393−8.
14. Kinnear D, Morrison J, Allan L, Henderson A, Smiley E, Cooper SA. Prevalence of physical conditions and multimorbidity in a cohort of adults with intellectual disabilities with and without Down syndrome: cross-sectional study. BMJ Open. 2018 Feb;8(2):e018292.
15. Bayen E, Possin KL, Chen Y, Cleret de, Langavant L, Yaffe K. Prevalence of aging, dementia, and multimorbidity in older adults with Down syndrome. JAMA Neurol. 2018 Nov;75(11):1399−406.
16. Ueda K, Okamoto N, Hirayama S, Tatsumi J, Sagawa S. Daunshoukougun wo motsu seijin no kenkoukanri ni kansuru chousa: himan to metaborikkushindoromu ni chakumoku shite [Health status and health management of adults with Down syndrome: obesity and metabolic syndrome]. Nichiidenkaunseringukaishi [Jap J Genet Couns]. 2011;32(3):101−7. Japanese.
17. Examination committee of criteria for 'obesity disease' in Japan; Japan society for the study of obesity. New criteria for 'obesity disease' in Japan. Circ J. 2002 Nov;66:987−92.
18. Japan Society for the Study of Obesity. Guidelines for the management of obesity disease 2016. Tokyo: Life Science Publishing; 2016. Chapter1-2; p. 1−17. Japanese.
19. World Health Organization. ICD-10 Version: 2019 [Internet]. World Health Organization; 2019. [cited 2022 Feb 17]. Available from: https://icd.who.int/browse10/2019/en
20. Lavigne J, Sharr C, Elsharkawi I, et al. Thyroid dysfunction in patients with Down syndrome: results from a multi-institutional registry study. Am J Med Genet A. 2017 Jun;173(6):1539−45.
21. Bell AJ, Bhate MS. Prevalence of overweight and obesity in Down's syndrome and other mentally handicapped adults living in the community. J Intellect Disabil Res. 1992 Aug;36:359−64.
22. Tsou AY, Bulova P, Capone G, et al. Medical care of adults with Down syndrome: a clinical guideline. JAMA. 2020 Oct;324(15):1543−56.
23. Carfì A, Vetrano DL, Mascia D, et al. Adults with Down syndrome: a comprehensive approach to manage complexity. J Intellect Disabil Res. 2019 Jun;63(6):624−9.
24. Prasher V, Gomez G. Natural history of thyroid function in adults with Down syndrome-10-year follow-up study. J Intellect Disabil Res. 2007 Apr;51(4):312−7.
25. Fuller RW, Luce MW, Mertz ET. Serum uric acid in mongolism. Science. 1962 Sep;137(3533):868−9.
26. Okabe H, Mizuguchi M, Hosoya T, et al. Daunshoukougun ni gappeisuru tsufu, kounyousankesshou no kentou [Hyperuricemia and gout in Down's syndrome]. Tsufu to Kakusantaisya [Gout Nucleic Acid Metab]. 2004; 28(1):19−26. Japanese.
27. Kashima A, Higashiyama Y, Kubota M, Kawaguchi C, Takahashi Y, Nishikubo T. Children with Down's syndrome display high rates of hyperuricaemia. Acta Paediatr. 2014 Aug;103(8):e359−64.
28. Niegawa T, Takitani K, Takaya R, et al. Evaluation of uric acid levels, thyroid function, and anthropometric parameters in Japanese children with Down syndrome. J Clin Biochem Nutr. 2017 Sep;61(2):146−52.
29. Žitňanová I, Korytár P, Aruoma OI, et al. Uric acid and allantoin levels in Down syndrome: antioxidant and oxidative stress mechanisms? Clin Chim Acta. 2004 Mar;341 (1-2):139−46.
30. Garlet TR, Parisotto EB, de Medeiros Gda S, et al. Systemic oxidative stress in children and teenagers with Down syndrome. Life Sci. 2013 Oct;93(16):558−63.
31. Carfì A, Romano A, Zaccaria G, et al. The burden of chronic disease, multimorbidity, and polypharmacy in adults with Down syndrome. Am J Med Genet A. 2020 May;182(7):1735−43.
32. Real de, Asua D, Quero M, Moldenhauer F, Suarez C. Clinical profile and main comorbidities of Spanish adults with Down syndrome. Eur J Intern Med. 2015 Jul;26(6): 385−91.
33. Osako M, Takeuchi C, Mochizuki Y. Shounikihasshoushinkeikeishikkan wo yusuru kanja no shounika kara seijinshinryouka eno ikou: chiteki undoushougai wo tomonau kanja eno torikumi [Transition from pediatric to adult health care in patients with childhood-onset neurological disease: clinical practice for individuals with intellectual and physical disabilities]. Shinkeichiryou [Neurol Therap]. 2021 Mar;38(2):112−22. Japanese.
34. Skotko BG, Kishnani PS, Capone GT, Down Syndrome Diagnosis Study Group. Prenatal diagnosis of Down syndrome: how best to deliver the news. Am J Med Genet A. 2009 Nov;149A(11):2361−7.
35. Skotko BG, Capone GT, Kishnani PS, Down Syndrome Diagnosis Study Group. Postnatal diagnosis of Down syndrome: synthesis of the evidence on how best to deliver the news. Pediatrics. 2009 Oct;124(4):e751−8.
36. Sheets KB, Crissman BG, Feist CD, et al. Practice guide-

lines for communicating a prenatal or postnatal diagnosis of Down syndrome: recommendations of the national society of genetic counselors. J Genet Couns. 2011 Oct;20(5): 432–41.

(Received, October 6, 2022)
(Accepted, December 28, 2022)
(J-STAGE Advance Publication, February 21, 2023)