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ORIGINAL ARTICLE

Health-related Quality of Life in Adult Patients with Multiple Epiphyseal Dysplasia and Spondyloepiphyseal Dysplasia

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Objectives: Multiple epiphyseal dysplasia (MED) and spondyloepiphyseal dysplasia (SED) are skeletal dysplasias associated with premature osteoarthritis and short stature. Patients with SED often have spinal and ocular problems. Few reports have focused on the health-related quality of life (HRQoL) of patients with skeletal dysplasias associated with premature osteoarthritis. The purpose of this study was to evaluate the HRQoL of adult patients with MED and SED. **Methods:** Questionnaires covering demographics, medical history (cataract, retinal detachment, and osteoarthritis), surgical history (osteotomy and arthroplasty), and the Short Form-36 (SF-36) health survey were sent to all patients with MED and SED with medical records at the investigators' institutions. Among the 27 patients who completed the questionnaire, patients aged 20 years or older were included in this cohort. **Results:** The subjects were 18 affected individuals. The physical component summary score (PCS) was significantly lower in the MED and SED groups than in the normal population and tended to deteriorate with age. Conversely, there was a positive correlation between the mental component summary score and age. The role/social component summary score was not correlated with age. MED patients with osteoarthritis had a low PCS. PCS was particularly low in two SED patients with a medical history of cataract, whereas there was no association with a history of retinal detachment or osteoarthritis. **Conclusions:** The physical domain of HRQoL in MED and SED patients significantly deteriorated at a young age. Appropriate medical management of these skeletal dysplasias is required not only for orthopedic functions but also for ocular problems.

Key Words: multiple epiphyseal dysplasia; quality of life; SF-36; spondyloepiphyseal dysplasia

INTRODUCTION

Multiple epiphyseal dysplasia (MED) and spondyloepiphyseal dysplasia (SED) are heterogeneous skeletal dysplasias associated with premature osteoarthritis.[1–3] Malformed and restricted joints in MED and SED lead to severe pain, contracture, and ligament laxity. Joint deformity results in early osteoarthritis, often requiring joint replacement early in life.[4] To prevent early osteoarthritis, some patients undergo osteotomy to realign the lower extremities.[5,6] In addition to early osteoarthritis, MED is characterized by a disproportionate short stature.[7] As well as premature

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osteoarthritis, orthopedic problems in SED include disproportionate short stature, scoliosis, odontoid hypoplasia, and atlantoaxial instability.[3] Most patients with SED also have hearing problems and ocular problems such as myopia, cataract, and retinal detachment.[8]

The health-related quality of life (HRQoL) is a useful indicator of the overall health of individuals and covers physical, mental, and social health. In the field of skeletal dysplasia, HRQoL has been evaluated in adult patients with osteogenesis imperfecta[9,10] and achondroplasia.[11,12] The HRQoL for both disorders demonstrated a physical domain lower than that in the normal population. The patients' physical function also deteriorated in skeletal dysplasias associated with short stature.[13,14] However, the HRQoL of MED and SED has not yet been fully elucidated. In this study, we investigated HRQoL in patients with MED or SED. We addressed both disorders together as skeletal dysplasias with premature osteoarthritis; the reason for this was that we had access to only a small cohort of subjects with these rare disorders. We evaluated HRQoL in a Japanese cohort of adult patients with MED or SED and identified the relationship between disease-specific complications and HRQoL for these disorders.

MATERIALS AND METHODS

Participants

This cross-sectional study was approved by the institutional review board of the relevant institutions (Nagoya University Hospital, the University of Tokyo Hospital, and Osaka University Hospital) (reference number: 2015-0412), and data were collected from July 2016 to March 2018. Informed consent was obtained from all participants included in the study. The eligibility criteria were a diagnosis of MED or SED based on characteristic clinical and radiological findings; age 20 years or older; and a history of visiting Nagoya University Hospital, the University of Tokyo Hospital, or Osaka University Hospital. A questionnaire, a description of the study rationale, and an informed consent form were sent to each of the eligible patients. The questionnaire included questions on general demographics, disease-specific medical history, and HRQoL. Each participant was given a ¥500 gift card as a participation incentive after completing and returning the written questionnaire and consent form.

Questionnaire on Demographics and Medical History

The front cover of the questionnaire included entry columns for signature, date of birth, and registration date. The general demographics included recent height and weight, educational history, marital status, and family history of MED and SED. The subjects' education level was classified according to the International Standard Classification of Education. Complications, including cataract, retinal detachment, and osteoarthritis, and a surgical history of osteotomy and arthroplasty were analyzed as the disease-specific medical history.

Evaluation of Health-related Quality of Life

In the current study, the Short Form-36 (SF-36)[15] health survey was used to evaluate HRQoL. SF-36 is widely employed to analyze separately the HRQoL of the physical, mental, and social domains, and it has been validated for use in Japan.[16,17] SF-36 comprises 36 questions for evaluating eight subscales, including physical functioning, role functioning (physical), role functioning (emotional), bodily pain, general health, vitality, social functioning, and mental health. Based on these subscales, three component summary scores [the physical component summary score (PCS), the mental component summary score (MCS), and the role/social component summary score (RCS)] were calculated.

Statistics

Comparison of the PCS, MCS, and RCS scores between the study subjects and the Japanese standard values was performed using the z-test. Correlation analysis was performed between age and PCS, MCS, and RCS. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

Participants

The questionnaires were sent to 51 patients whose medical records were identified at one of the three institutions (Nagoya University Hospital, the University of Tokyo Hospital, or Osaka University Hospital) and contained their address. Twenty-seven patients completed and returned the questionnaires; however, nine patients under 20 years of age were excluded. Finally, 18 patients were included in the current study (**Table 1**).

Patient Demographics

The participants' demographic data are shown in **Table 2**. The mean age was 32.4 years in the MED group and 41.8 years in the SED group. The average z-scores for height

Table 1. Participants' data

Case	Disease	Age (years)	Sex	Height (cm)	BMI (kg/m^2)	Education level	Married	Family history	Medical history			Surgical history		PCS	MCS	RCS
									Cataract	Retinal detachment	OA	Osteotomy	Arthroplasty			
1	MED	36	Female	143	23.47	Tertiary	Yes	No	No	No	Yes	Yes	No	36.65	53.22	59.62
2	MED	24	Male	167	22.59	Tertiary	No	No	No	No	No	Yes	No	43.73	25.64	36.4
3	MED	37	Male	177	19.15	Tertiary	Yes	Yes	No	No	No	No	No	46.41	64.32	53.58
4	MED	37	Female	159	25.71	Post-secondary or short-cycle tertiary	No	No	No	No	Yes	Yes	No	33.36	52.25	62.45
5	MED	28	Female	144	19.29	Post-secondary or short-cycle tertiary	No	No	No	No	Yes	No	Yes	28.57	44.13	39.12
6	SED	65	Male	151	24.13	Tertiary	Yes	No	No	No	Yes	No	No	25.28	61.21	59.72
7	SED	44	Male	130	22.49	Tertiary	No	Yes	No	No	Yes	No	Yes	40.82	55.47	59.66
8	SED	28	Male	146	31.90	Upper secondary	No	Yes	No	No	Yes	No	No	35.12	33.62	64.68
9	SED	22	Female	118	25.14	Upper secondary	No	No	No	No	No	No	No	37.09	51.87	60.62
10	SED	22	Male	140	29.08	Upper secondary	No	No	No	Yes	No	Yes	No	26.58	51.97	51.13
11	SED	49	Female	133	22.65	Post-secondary or short-cycle tertiary	Yes	No	No	No	No	No	No	–6.65	61.46	70.17
12	SED	42	Female	142	21.82	Tertiary	No	Yes	No	Yes	Yes	No	No	37.02	37.62	66.22
13	SED	68	Female	140	22.45	Upper secondary	Yes	Yes	Yes	Yes	Yes	No	No	13.99	50.3	71.34
14	SED	20	Female	112	19.93	Post-secondary or short-cycle tertiary	Yes	No	No	No	Yes	No	No	14.77	38.2	33.95
15	SED	31	Male	140	33.16	Tertiary	No	No	No	No	No	No	No	6.68	54.68	60.99
16	SED	31	Male	142	20.83	Tertiary	No	No	No	No	Yes	No	No	60.28	51.96	49.58
17	SED	44	Male	135	26.89	Tertiary	No	No	No	No	Yes	No	No	50.83	60.63	47.98
18	SED	77	Male	148	23.28	Lower secondary	Yes	No	Yes	No	Yes	No	No	1.03	57.74	16.66

BMI, body mass index; OA, osteoarthritis; PCS, physical component summary; MCS, mental component summary; RCS, role/social component summary; MED, multiple epiphyseal dysplasia; SED, spondyloepiphyseal dysplasia.

Table 2. Demographics of the MED and SED groups

	MED	SED
Patients (n)	5	13
Age (years, mean ± SD)	32.4 ± 6.0	41.8 ± 18.7
Sex (no, female/male)	3/2	6/8
Z-score for height (mean ± SD)	–1.0 ± 1.7	–5.2 ± 1.7
BMI (kg/m^2, mean ± SD)	22.0 ± 2.8	24.9 ± 4.2
Education level		
Lower secondary (n)	0	1
Upper secondary (n)	0	4
Post-secondary or short-cycle tertiary (n)	2	2
Tertiary (n)	3	6
Married (%)	40.0	38.5
Family history (%)	20.0	30.1

and the BMI were –1.0 and 22.0 kg/m^2, respectively, in the MED group, and –5.2 and 24.9 kg/m^2, respectively, in the SED group. Of the 18 subjects, 1 was educated to the lower secondary level, 4 to the upper secondary level, 4 to the post-secondary or short-cycle tertiary level, and 9 to the tertiary level. Moreover, 38.9% were married, and 27.8% had a family history of skeletal dysplasia.

Influence of Disease and Age on HRQoL

Figure 1A shows the PCS, MCS, and RCS in MED and SED patients with reference to Japanese standard values. The mean PCS of the patients with these disorders was significantly lower than the standard value, whereas there was no statistical difference in MCS and RCS scores between the patients and the standard population (**Fig. 1A**). The patients' PCS scores were significantly below the standard scores for those younger than 40 years, and the scores decreased further for those older than 40 years (**Fig. 1B**). There were no statistical differences in the MCS and RCS scores between our patients and the standard population for either age group. PCS tended to deteriorate with age (**Fig. 1C**), whereas there was a significant positive correlation between MSC and age (**Fig. 1D**). The RCS was not correlated with age (r = 0.001; P = 0.996).

Influence of Ocular Complications and Osteoarthritis on HRQoL

When the relationship between medical complications and PCS was evaluated in the MED and SED groups combined, lower PCS scores were associated only with cataract (**Fig. 2A**), but not with retinal detachment or osteoarthritis. In the MED group, however, the PCS in patients with osteoarthritis was below the average (**Fig. 2B**). Cataracts were seen in two SED patients only. Their PCS scores were much lower than other individuals with SED (**Fig. 2C**).

DISCUSSION

We demonstrated that the physical domain score of HRQoL was low and tended to decrease with age in adult patients with MED and SED. However, conversely, the MCS of these patients increased with age. In the current study, a medical history of cataract was correlated with reduced PCS. In MED patients, PCS was lower in those with osteoarthritis. The role/social domain score was not correlated with these skeletal dysplasias.

Dhiman et al.[14] evaluated the SF-12 health survey in members of Little People of America (LPA), which included 14 patients with SED from a total of 189 individuals with short stature. In the LPA study, PCS was significantly lower in patients with SED and diastrophic dysplasia relative to those with achondroplasia. However, pain was associated with poor physical function in the population with skeletal dysplasia.[13] More patients with SED and diastrophic dysplasia experienced pain than those with achondroplasia.[14] In the current study, the average PCS score in MED and SED patients under 40 years of age was also approximately 10 points lower than that of contemporary Japanese achondroplasia patients.[11] Compared with the general population, the MED and SED groups showed significantly lower physical quality of life (QoL) from a younger age, probably due to the pain associated with premature osteoarthritis.

The patients' PCS remained at a low level even after arthroplasty and osteotomy (**Table 1**). Osteoarthritis is a

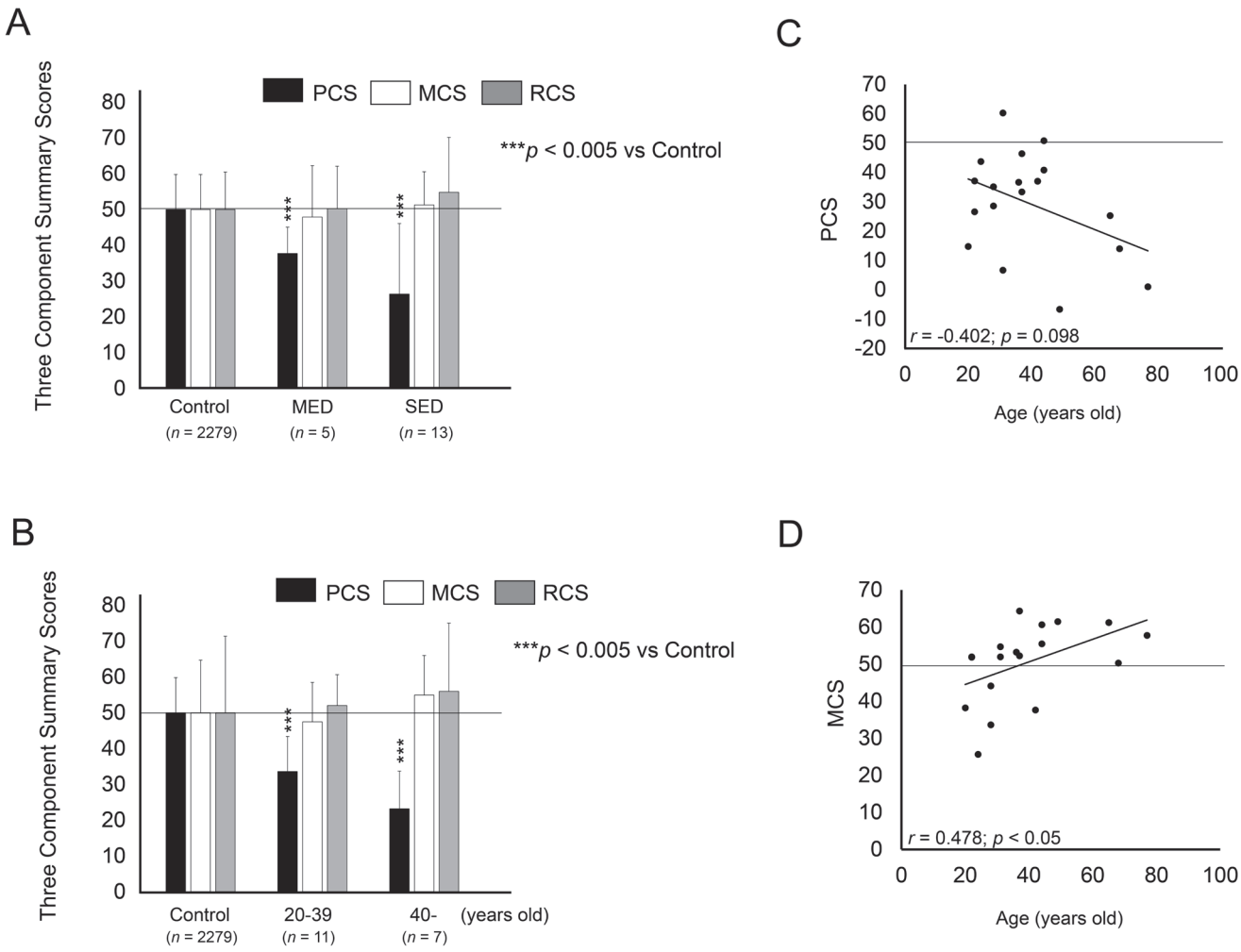

Fig. 1. Three component summary scores of participants. (A) The graphs show physical component summary (PCS), mental component summary (MCS), and role/social component summary (RCS) scores of MED and SED patients. Means and SDs are indicated. (B) The graphs show PCS, MCS, and RCS for each age group. Means and SDs are indicated. (C) Scatter diagram shows PCS and age. The correlation line is indicated. (D) Scatter diagram shows MCS and age. The correlation line is indicated.

common disease in the general population, and it has a significant impact on HRQoL. Arthroplasty plays a limited, but significant, role in improving the quality of life.[18] MED and SED patients require arthroplasty at younger ages. Based on relatively large cohorts reported by two groups, the average age at the time of total hip arthroplasty was under 40 years, i.e., 32 years in MED patients[19] and 39 years in SED patients.[20] In both groups, arthroplasty reduced pain and improved QoL in patients with skeletal dysplasia, but the quantitative outcomes were less marked than those reported after arthroplasty in patients without these skeletal dysplasias because of the high incidence of complications related to these conditions. To delay the onset of premature osteoarthritis, various osteotomies have been indicated for correcting deformities.[5,6] Growth modulation procedures through hemiepiphysiodesis were also employed at the growth plates of the distal femur and proximal tibia in patients before skeletal maturity.[21] However, the long-term results of these realignment procedures remain unproven.

There seem to be no data on HRQoL regarding retinal detachment, although vision-related QoL was impaired after retinal detachment surgery.[22] Moreover, cataract surgery was not associated with improvement in SF-36 scores.[23] In patients with rheumatoid arthritis, it has been reported that ocular manifestations, including cataract, were associated with a significant negative impact on PCS.[24] In acute ante-

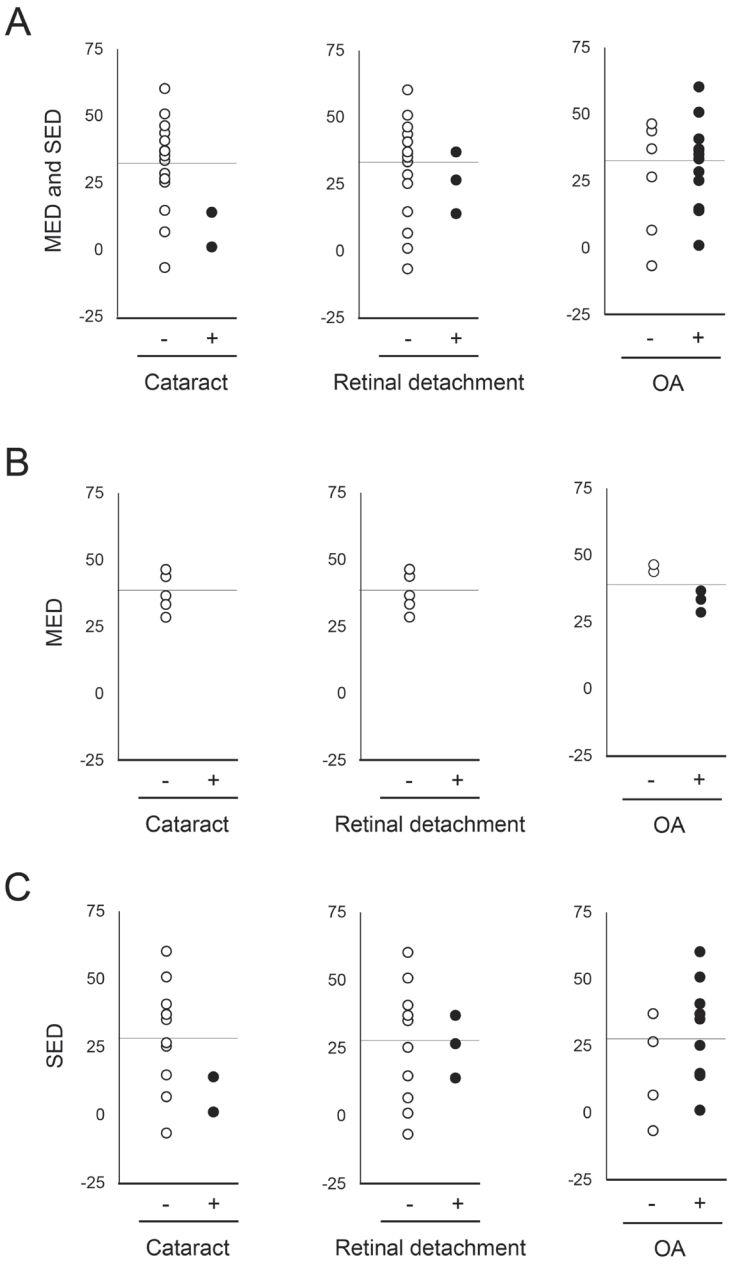

Fig. 2. Physical component summary (PCS) scores for each complication. (A) The scatter graphs show PCS scores in patients with cataract, retinal detachment, and osteoarthritis (OA) in the MED and SED groups combined (A), MED group only (B), and SED group only (C). Bars indicate the mean PCS scores in each group.

rior uveitis, which is often associated with the *HLA-B27* gene in patients with or without spondyloarthritis, the physical domain of SF-36 significantly deteriorated over 5 years.[25] Cataract could impair physical function in patients with musculoskeletal disorders; indeed, lower PCS scores were observed in SED patients with cataract than in those without cataract.

In the current study, older patients had higher MCS scores, whereas PCS scores decreased with age. Similar results, i.e., the combination of a high MCS and a low PCS, were previously demonstrated in patients with severe osteogenesis imperfecta[9,10,26,27] and in those with achondroplasia in the lower height group (less than 120 cm).[11] Physical function may not always be correlated with mental function in patients with skeletal dysplasias.

This study has several limitations. First, the number of

participants was limited, and bias resulted because participants were selected from three university hospitals that held their medical records; consequently, subjects were not representative of the country as a whole. A larger number of participants is required to draw firm conclusions regarding these rare diseases. Second, the data analyzed in the current study were based on questionnaires. Self-reported descriptions are not always accurate with respect to disease-specific complications and past surgical interventions. Third, details relating to spinal conditions were not included in the questionnaire. Because PCS tended to be lower in SED patients than in MED patients, adding neurological complications to the analysis would reveal the effect of spinal deformity on PCS in SED patients. Fourth, although MED and SED have broad phenotypes, patients were not classified according to their genetic abnormalities. Because genetic testing for these diseases is not covered by insurance, clinical and radiological diagnoses remain the gold standards in Japan.

CONCLUSION

Physical function in adult patients with MED and SED was lower than for the unaffected population and decreased with age. Appropriate medical management for these skeletal dysplasias is required not only for orthopedic function but also for ocular problems.

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CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to disclose.

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