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ORIGINAL RESEARCH

Physical, Mental, and Social Problems of Adolescent and Adult Patients with Achondroplasia

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Abstract

Patients with achondroplasia (ACH) require various medical interventions throughout the lifetime. Survey of health-related quality of life (HRQoL) in adult ACH patients is essential for the evaluation of treatment outcomes performed during childhood such as growth hormone administration and limb lengthening surgeries, but no study focused on the treatment strategy by analyzing HRQoL of ACH patients. The purpose of this study was to assess whether final height impacted on HRQoL and to evaluate what kinds of medical interventions were positively or negatively associated with HRQoL. We included 184 ACH patients (10–67 years old) who were registered in the patients' associations or who had a medical history of the investigators' institutions, and analyzed HRQoL by using Short Form-36 and patient demographics. Physical component summary (PCS) was significantly lower than the standard values in each age, especially in elderly populations, while mental component summary (MCS) was similar to the standard values. Role/social component summary was deteriorated only in elderly populations. The PCS was improved in the patients who had a height of 140 cm or taller ($p < 0.001$). The PCS and MCS were strongly associated with the past medical history of spine surgeries ($p < 0.001$ and $p = 0.028$, respectively). A treatment strategy would be planned to gain a final height of 140 cm or taller during childhood in combination with growth hormone administration and limb lengthening surgeries. Appropriate medical management for neurological complications of adult ACH patients is required to maintain physical and mental function.

Keywords Achondroplasia · SF-36 · Quality of life · Height · Limb lengthening · Spine

Introduction

Achondroplasia (ACH) is the most common form of short-limbed short stature, with an incidence of 1 in 16,000–26,000 live births [1]. ACH is characterized by rhizomelic shortening of the extremities, characteristic facies with frontal bossing and midface hypoplasia, increased lumbar lordosis, limitation of elbow extension, and trident hand [2]. This disorder is caused by gain-of-function mutations in fibroblast growth factor receptor 3 (FGFR3), which is a negative regulator of longitudinal bone growth [3, 4]. In ACH children, mild to moderate hypotonia is common and motor milestones are usually delayed, and abnormalities at the craniocervical junction sometimes require surgical decompression. Otolaryngological complications such as otitis media and upper airway obstruction often require the insertion of ventilation tubes or adenotonsillectomy. Spinal canal stenosis (SCS) is a serious neurological complication of adult ACH [5]. Obesity is another major problem which aggravates the morbidity associated with SCS and contributes to the nonspecific joint problems and to the early cardiovascular mortality. The overall mortality and age-specific mortality at all ages remained significantly increased.

Although there are currently no molecular-targeted therapies to suppress FGFR3 signaling, subcutaneous recombinant human growth hormone administration [6, 7] and limb

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lengthening surgeries [8, 9] are therapeutic options in some limited countries for short stature in ACH children. Moreover, various above-mentioned physical impairments other than short stature require periodic medical follow-up throughout the patients' lifetime. Additionally, patients with ACH suffer from mental or social consequences as well as physical impairments. Health-related quality of life (HRQoL) is a useful indicator of overall health of individuals including physical, mental, and social health [10]. Measurement and analysis of HRQoL in adult individuals with ACH are essential for the evaluation of treatment outcomes performed during childhood. Few studies, however, focused on HRQoL of ACH patients [11–14]. Additionally, there seems to be no study focusing on the treatment strategy for achondroplasia by analyzing HRQoL of ACH patients. Therefore, we aimed to compare the HRQoL of ACH patients aged 10 years or older with general Japan population values, to assess whether growth hormone administration and limb lengthening surgeries impact on HRQoL, and to evaluate what kinds of medical interventions are positively or negatively associated with HRQoL.

Materials and Methods

Eligible Patients

This study was cross-sectional survey approved by institutional review board in our each institution. The data were collected from July 2016 to March 2018. Among the ACH patients who had a medical history at an either institution of Nagoya University Hospital, the University of Tokyo Hospital or Osaka University Hospital, or who were registered to the patients' association of ACH in Japan (Tukushinokai or Tsukushinbo), we recruited the patients aged 10 years or older (Fig. 1a). The eligible patients received a description of study rationale and a consent form. If the patients were less than 20 years old, their parent wrote a consent form and questionnaires as a representative. We sent a questionnaire to the patients who had a written informed consent form. The questionnaire composed of the HRQoL, general demographics questionnaire, and disease-specific medical history measurement. Patients who responded the questionnaire were given a gift card for 500 yen as a participation incentive.

Questionnaire

The front cover of questionnaire provided entry columns of signature, birthday, and registered date. The general demographics questionnaire included recent height and weight, educational history, and marital status. Level of education was determined on the basis of the International Standard Classification of Education (ISCED). The items of the disease-specific past medical history composed of growth hormone therapy, limb lengthening surgeries, orthodontic treatments, otolaryngological surgeries, foramen magnum decompression, and spine surgeries. There were also questions about social welfare such as a use of nursing care service or a wheelchair or not. Additionally, activities of daily living (ADL) including 'getting in and out of vehicles' and 'stepping the stairs' were analyzed with three-grade evaluation: impossibility is 0 score, difficulty is 0.5 score, and ease is 1 score.

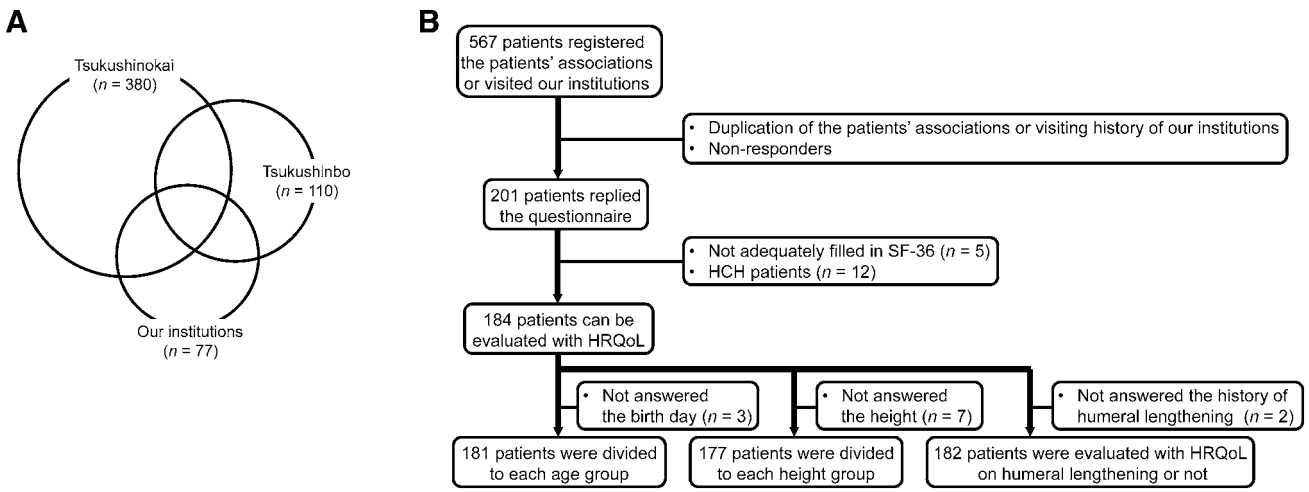

Fig. 1 The flowchart of included patients. The 380 and 110 patients belong to Tsukushinokai and Tsukushinbo of the patients' associations in Japan, respectively, and the 77 patients have a treatment history in our institutions (**a**). Although the cumulative total number of the eligible patients is 567, the 201 patients returned the questionnaires. The 184 patients were evaluated after excluded patients without fully completed SF-36 or with HCH. Each analysis was performed after the following exclusions: no filling birth day, height, and treatment history of humeral lengthening, respectively (**b**)

Health-Related Quality of Life Measure

The HRQoL was assessed with the Short Form-36 (SF-36) [10]. SF-36 is widely used to assess physical and mental well-being in social and individual contexts. It consists of multiple question items for measuring eight subscales, including physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, and mental health. The SF-36 has been validated for use in Japan [15, 16]. From the eight subscales, we can calculate three component summary scores including Physical Component Summary (PCS) (50.0 ± 9.8, range − 13.5 to 81.5), mental component summary (MCS) (50.0 ± 9.8, range 12.1 to 77.2), and role/social component summary (RCS) (50.0 ± 10.5, range − 4.8 to 82.0) based on the Japanese standard values. Higher scores indicate better HRQoL.

Patient Inclusion

We sent the questionnaires to 567 patients who were registered in the Patients' associations (Tsukushinokai or Tsukushinbo) or who had a medical history of our institutions (Nagoya University Hospital, the University of Tokyo Hospital, or Osaka University Hospital) (Fig. 1a). Patients who received duplicate questionnaires responded only once. Among 201 patients who had returned the questionnaire, 12 hypochondroplasia (HCH) patients and five patients with an inadequate response to SF-36 were excluded. Finally, the HRQoL from 184 ACH patients can be evaluated (Fig. 1b). Subgroup analyses were performed for each age (every 10-year-old) and final height (every 10 cm) group, respectively.

Statistics

We employed analysis of variance (ANOVA) for the PCS, MCS, and RCS of each age group of 10–19, 20–29, 30–39, 40–49, 50–59, and 60–69 years and each height group of 100–109, 110–119, 120–129, 130–139, 140–149, and 150–159 cm followed by Tukey's post hoc test. Comparison between the patients and Japanese standard value was done with *z* test in each age group except for the 10–19 years of age group, since there was no normative data of this age group. Comparison of the PCS, MCS, and RCS was also done in each height group. Student *t* test was carried out for analyzing specific variables on the social welfare and on ADL between patients with the height of 100–139 cm and that of 140–159 cm. The level of statistical significance was defined as $p < 0.05$.

We performed multiple linear regression analysis to assess the influence of past medical treatment (growth hormone, tibial, and femoral lengthenings) on height and past

Table 1 Patient demographics for each age group

Characteristic	10–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years
n	73	46	34	15	8	5
Sex, f/m (*n*)	35/38	29/16	17/17	10/5	8/0	4/1
Height (cm)	125.1 ± 13.6	132.8 ± 11.1	135.8 ± 10.8	128.8 ± 7.9	122.7 ± 8.1	123.4 ± 8.3
BMI (kg/m^2)	24.6 ± 5.3	27.1 ± 5.6	26.3 ± 6.0	29.5 ± 5.8	27.7 ± 6.2	29.7 ± 4.0
Education level						
Lower secondary (*n*)	0	2	2	0	0	1
Upper secondary (*n*)	3	11	11	7	5	2
Post-secondary or short-cycle tertiary (*n*)	0	7	10	7	1	0
Tertiary (*n*)	0	10	9	1	1	2
Currently student (*n*)	68	15	2	0	0	0
No response (*n*)	2	1	0	0	1	0
Marital status (%)	0.0	2.3	17.6	46.7	37.5	60.0
Treatment history						
Growth hormone (%)	84.9	84.8	44.1	14.3	25.0	0.0
Tibial lengthening (%)	50.7	60.9	70.6	66.7	25.0	0.0
Femoral lengthening (%)	28.2	36.0	58.8	60.0	12.5	0.0
Humeral lengthening (%)	16.9	21.7	26.5	0.0	0.0	0.0
Orthodontics (%)	34.7	22.2	19.4	0.0	42.9	0.0
Adenoidectomy (%)	30.1	23.9	11.8	6.7	12.5	0.0
Ear ventilation tubing (%)	41.1	32.6	11.8	6.7	0.0	0.0
Foramen magnum surgery (%)	24.7	17.4	11.8	7.1	25.0	20.0
Spine surgery (%)	4.2	19.6	33.3	57.1	87.5	20.0

The values of height and BMI given as the mean ± SD

BMI body mass index

medical treatments (height, humeral lengthening, orthodontic treatments, adenotonsillectomy, ear ventilation tubing, foramen magnum decompression, and spine surgery) on the PCS, MCS, and RCS. All statistical analyses were performed by using SPSS, version 23 (IBM Corporation, Armonk, NY).

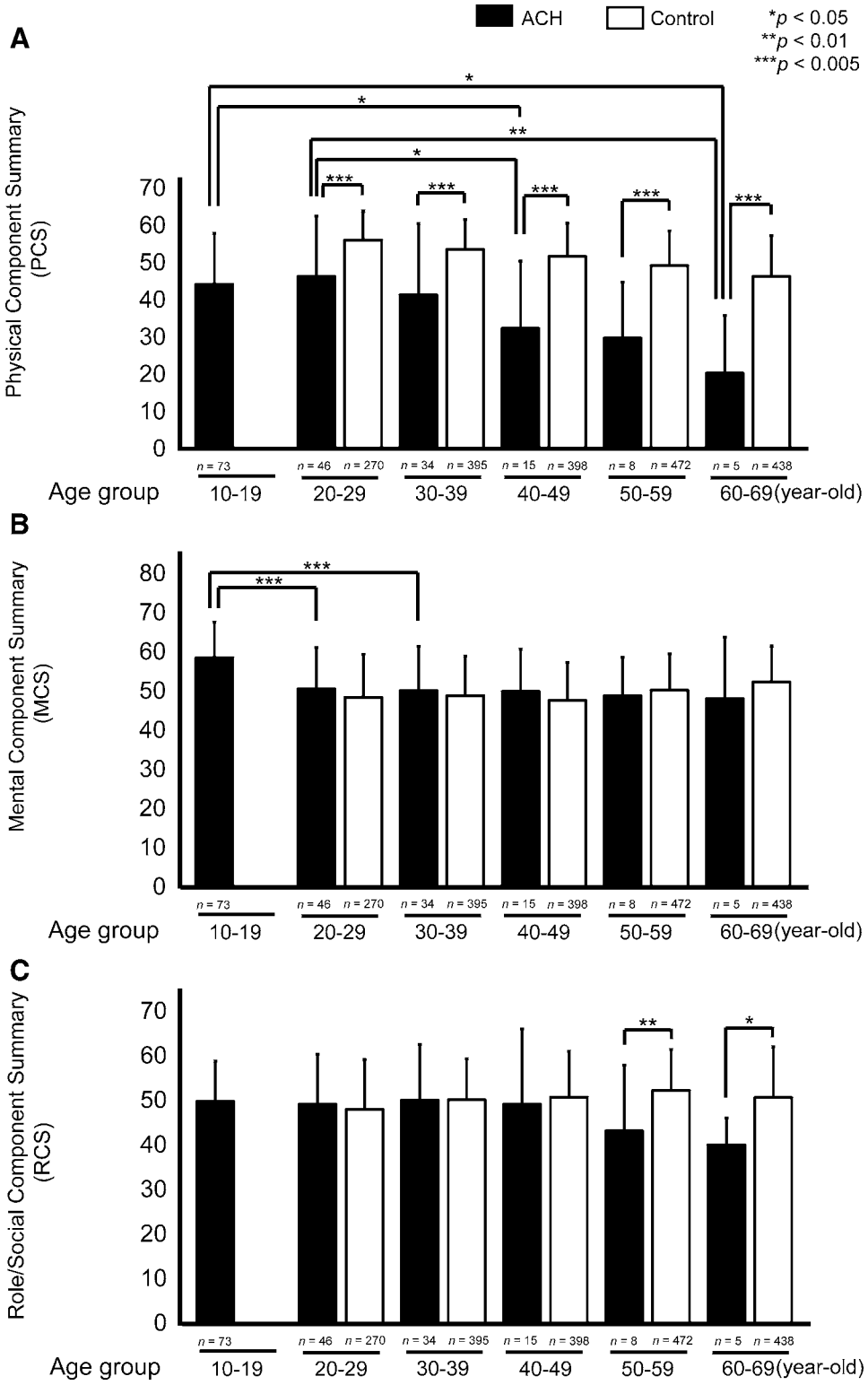

Fig. 2 Three component summary for each age group. The graphs show PCS (**a**), MCS (**b**), and RCS (**c**). Mean and SD are indicated. No Japanese standard values are available in the age group of 10–19-year-olds [15, 16]

Results

Comparison with General Japan Population Values

Patient's demographics in each age group are shown in Table 1. The ranges of age and height are 10 to 67 years and 100 to 157 cm, respectively. Figure 2 shows the PCS, MCS, and RCS in each age group in reference to Japanese standard values. Patients' PCS, which is gradually decreased with age, is significantly lower than the standard values in all age groups (Fig. 2a). The MCS of the adult patients, on the other hand, does not differ from the standard values in all age groups (Fig. 2b). Patients' RCS is also similar to the standard values in the group under 50 years old, but it is significantly lower in elderly populations (Fig. 2c).

Influence of Growth Hormone Administration and Limb Lengthening Surgeries on HRQoL

Table 2 shows the past medical treatments for short stature in ACH. Majority of patients underwent subcutaneous growth hormone treatment. Tibial and/or femoral lengthenings significantly contribute to the gain of the final height in ACH patients. Linear regression analysis of patients' final height by the past treatment history demonstrates significant positive effects of each treatment, especially of the lower limb lengthening (Table 3). The PCS, MSC, and RCS by patients' final height are shown in Fig. 3. The PCS is significantly lower than the standard value in the shorter patients' groups, but it does not differ from the standard value in the patients who have a height of 140 cm or taller (Fig. 3a). The MCS of the shorter patients (119 cm or less) is significantly higher than the standard value, but it does not differ from the standard value in taller height groups (Fig. 3b). There are no significant differences in the RCS in all height groups (Fig. 3c). ADL of the patients is analyzed between 100 and 139 cm and 140–159 cm of height groups (Table 4). Taller patients show significantly less uses of nursing care service and wheelchair and higher scores of three-grade evaluation of ADL than shorter patients.

Table 2 Treatment history for each height group

Height group	Growth hormone (%)	Tibial lengthening (%)	Femoral lengthening (%)
100–109 cm ($n=9$)	66.6	11.1	0.0
110–119 cm ($n=31$)	67.7	19.4	3.3
120–129 cm ($n=51$)	58.8	37.4	16.0
130–139 cm ($n=41$)	70.0	70.7	36.6
140–149 cm ($n=36$)	69.4	88.9	83.3
150–159 cm ($n=9$)	88.9	100.0	88.9

Table 3 Multiple linear regression analysis of height by each treatment

	Partial regression coefficient (95% CI)	p
Growth hormone	3.34 (0.33, 6.35)	0.030
Tibial lengthening	7.27 (3.40, 11.13)	<0.001
Femoral lengthening	11.57 (7.56, 15.58)	<0.001

Medical Interventions Associated with HRQoL

Finally, we analyze the relationship between the PCS, MCS, and RCS and past medical treatments, including height, humeral lengthening, and orthodontic, otolaryngological and orthopaedic surgeries (Table 5). In addition to the association between height and PCS, the PCS and MSC are strongly associated with the past spine surgeries such as laminectomy, laminoplasty, and instrumentation surgery for spinal canal stenosis.

Discussion

We evaluated HRQoL in a large group of patients with ACH and analyzed which factors positively or negatively affected HRQoL. Our study showed that ACH negatively affected HRQoL with a considerable effect on physical domain and to a small degree on social domain. Patients who had a height of 140 cm or taller showed significant elevated PCS scores. In addition, these patients could achieve elevated ADL including 'getting in and out of vehicles' and 'stepping the stairs' which resulted in decrease in nursing care. This indicated that a treatment strategy for short stature in ACH children would be planned to gain a final height of 140 cm or taller. Since growth hormone treatment, which was approved in some limited countries, not only provided inadequate therapeutic effects on longitudinal bone growth but also aggravated disproportion due to the greater increase in spinal height [17, 18], tibial and/or femoral lengthenings are needed in the current standard medical interventions [6, 19–21]. Actually, most patients who had a height of 140 cm or taller underwent limb lengthening procedures in the current study. This is the first study clearly describing the target height of ACH patients from the viewpoint of physical function.

Interestingly, a higher MCS score was observed in shorter patients' groups. Similarly, the QoL of osteogenesis imperfecta (OI), the brittle bone disease, documented that severely affected patients (OI type III) showed a higher MCS than mildly affected patients (OI type I) [22]. The difficulty of medical challenges from early life could contribute the

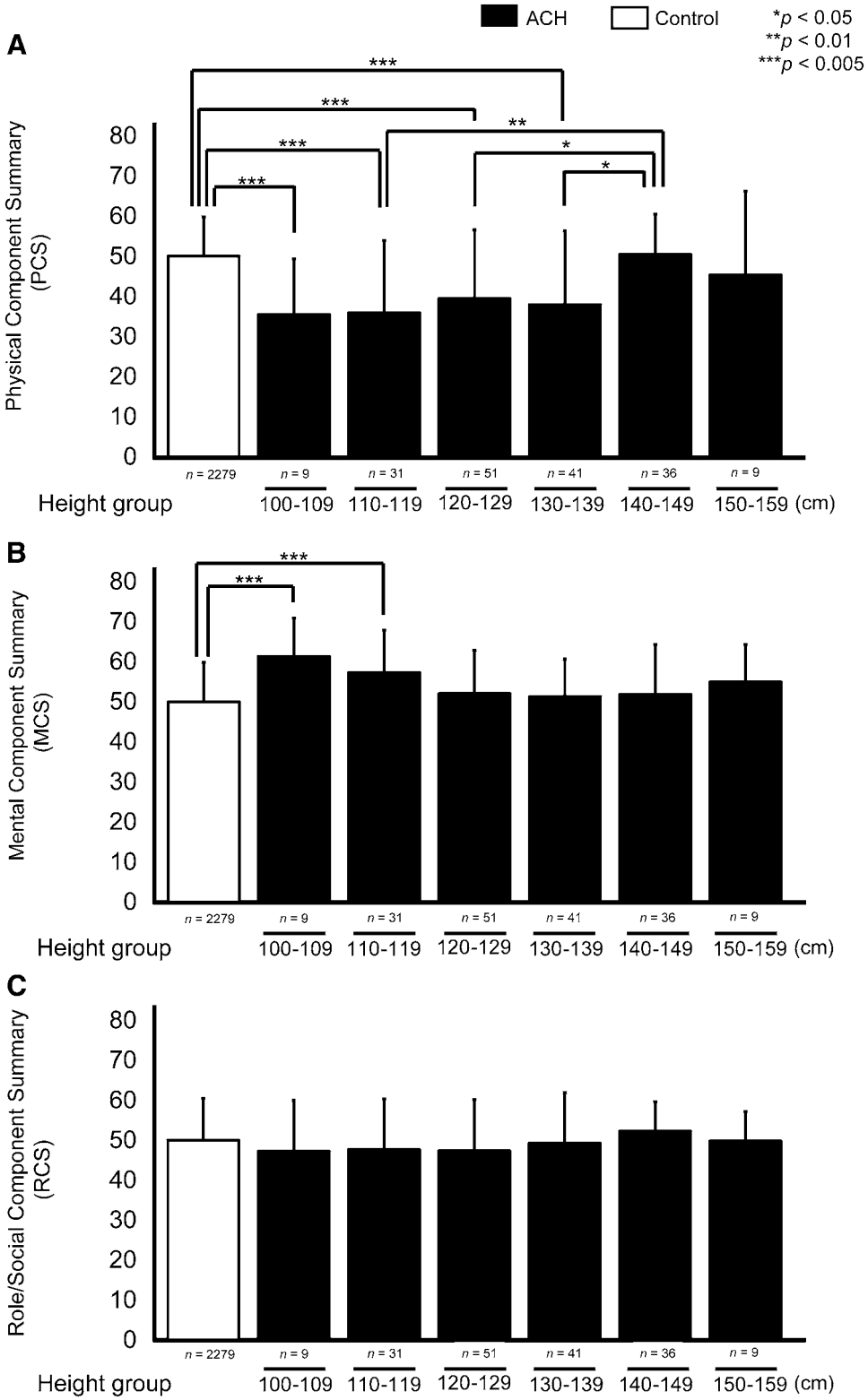

Fig. 3 Three component summary for each height group. The graphs show PCS (**a**), MCS (**b**), and RCS (**c**). Mean and SD are indicated

development of endurable and resilient characteristics in adult patients with severe types of OI [23]. It is suggested that physical disability is not necessarily correlated with mental function in congenital bone diseases.

We demonstrated that physical function of ACH patients deteriorated with age, but the MCS of the patients was similar to that of the general Japanese populations. The same pattern of differences was reported from the

Table 4 Activities of daily living for each height group

	100–139 cm	140–159 cm	*p*
n	130	45	
Age (year)	26.02 ± 15.07	25.60 ± 8.26	0.858
PCS	38.08 ± 17.20	49.42 ± 12.77	< 0.001
MCS	53.65 ± 10.66	52.47 ± 11.86	0.536
RCS	48.17 ± 12.63	51.77 ± 7.38	0.072
User			
Nursing care service (%)	10.24	0.00	0.033
Wheelchair (%)	19.70	2.22	0.005
ADL score			
Getting in and out of vehicles	0.75	0.92	< 0.001
Stepping the stairs	0.70	0.89	< 0.001

The values of age, PCS, MCS, and RCS given as the mean ± SD

PCS physical component summary, *MCS* mental component summary, *RCS* role/social component summary, *ADL* activities of daily living

research on the Little People of America (LPA) association [11, 14]. We should pay attention to the declination of physical function with age in ACH patients. Past spine surgery was significantly associated with physical function in elderly populations in the current study. Neurological impairments that required surgical interventions increased with age. Moreover, neurological symptoms sometimes persist after surgery. Actually, more than 70% of ACH patients complained of persistent back pain even after lumbar laminectomy and a similar pattern was evident in those who have had a cervical decompression or fusion [11]. This could be due to delay in spine surgery. For neurological complications in adult ACH patients, early surgical intervention may be considered in order to maintain QoL of elderly patients.

In regard to mental function, spine surgery was the only factor that affected decreased MCS score. A previous LPA study indicated that decreased MCS was associated with body pain [14]. Low MCS was also observed in other painful conditions such as sciatica and migraine [24]. Persistent pain associated with spinal disorders may reduce mental function of the patients. Appropriate medical intervention for neurological complications is important not only to maintain physical function but also improve mental function in ACH. Moreover, pain was more frequently complained in female ACH [13]. A QoL study for hereditary multiple exostosis, MCS, was also decreased in female compared with male [25], but the reason has not been explained exactly.

A previous LPA study indicated that the QoL in the social and economic domain was also decreased in patients with ACH, most of whom commented on disadvantages that related to public perceptions of their condition such as teasing, staring, inaccurate expectations, rudeness, and discrimination [12]. An anthropologist suggested that short-statured individuals were associated with a mystique not attributable to other types of physical and mental differences [26]. Actually, the decreased RCS was observed in elderly population in the current study. The RCS of younger populations, however, was not deteriorated probably due to improvement in social acceptance and supports compared with the past.

Satisfactory results have been reported in humeral lengthening for ACH [27, 28]. Long-term results and HRQoL, however, remain to be elucidated. In the current study, the number of patients treated with humeral lengthening was small. It was thus difficult to evaluate the effect of humeral lengthening on HRQoL. Further studies are needed to assess the effects of humeral lengthening on HRQoL, using different questionnaire forms of upper extremity such as a Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire [29].

There are several limitations. We could not compare patients' HRQoL to normal populations in the 10–19 years of age group, because SF-36 was not validated in this age group and Japanese standard values of the PCS, MCS, and RCS were not available. Second, there was a bias that majority of patients who participated in this survey was adolescent or young adult, resulting in few married people and inability to determine final academic backgrounds. Different results may have revealed if it was a survey to a higher age group.

Table 5 Partial regression coefficient after multiple linear regression analysis by each treatment

	PCS	*p*	MCS	*p*	RCS	*p*
Height	0.30	0.004	−0.12	0.125	0.06	0.441
Humeral lengthening	2.84	0.400	0.61	0.803	0.91	0.713
Orthodontics	1.11	0.685	2.22	0.270	−1.83	0.336
Adenotonsillectomy	−1.83	0.538	−2.28	0.295	3.23	0.140
Ear ventilation tubing	−3.28	0.229	2.62	0.189	−1.02	0.610
Foramen magnum surgery	−3.08	0.332	3.95	0.090	−4.34	0.064
Spine surgery	−17.38	< 0.001	−4.84	0.025	−1.60	0.457

PCS physical component summary, *MCS* mental component summary, *RCS* role/social component summary

Third, there was another bias that most of the patients in the present study belonged to the patients' associations. Fourth, patient variables such as height were self-reporting due to the questionnaire survey. Fifth, survey on otolaryngologic complications seemed to be inappropriate. A LPA study demonstrated that the PCS was decreased in patients with a past history of otolaryngological surgery [11], while otolaryngological interventions such as adenotonsillectomy and ear ventilation tubing did not affect the HRQoL in the current study. Different results could have been observed from a more detailed investigation. Finally, we lacked detail data on medication and surgeries, such as the duration of growth hormone administration and the amount of lengthening.

In conclusion, physical domain of HRQoL was decreased in ACH patients, especially in elderly populations, while mental domain was unchanged compared with general population values. Role/social domain of HRQoL was decreased only in elderly populations of ACH. A treatment strategy for short stature would be planned to gain a final height of 140 cm or taller during childhood in combination with growth hormone administration and limb lengthening surgeries. Appropriate medical management for neurological complications of adult ACH patients is required to maintain physical and mental function that deteriorate with age.

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Author Contributions MM, HK, KO, and NI designed the study. MM prepared the first draft of the paper. He is guarantor. KM, NH, SF, TK, and TK conducted the experimental work. SY was responsible for statistical analysis of the data. All authors revised the paper critically and approved the final version.

Compliance with Ethical Standards

Conflict of interest Masaki Matsushita, Hiroshi Kitoh, Kenichi Mishima, Satoshi Yamashita, Nobuhiko Haga, Sayaka Fujiwara, Keiichi Ozono, Takuo Kubota, Taichi Kitaoka, and Naoki Ishiguro have no commercial associations that might pose a conflict of interest in connection with the submitted article.

Human and Animal Rights and Informed Consent This study complied with ethical standards of research involving human participants and was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine (Reference Number: 2015-0412). Informed consent was obtained from all patients.

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