Table 1. Characteristics of Patients With Genotype A or a Non-A Genotype Acutely Infected With Hepatitis B Virus

Features	Genotype A (n = 107)	Non-A Genotypes (n = 105)*	*P* Value
Age (years)	36.3 ± 12.0	40.7 ± 14.3	0.032
Male sex	102 (95.3)	75 (71.4)	<0.001
HBeAg positive	104 (97.2)	79 (75.2)	<0.001
ALT (IU/L)	1210 ± 646	2225 ± 2851	0.045
Total bilirubin (mg/dL)	9.9 ± 9.4	7.5 ± 6.7	0.115
HBV DNA (log copies/mL)	7.0 ± 1.5	5.8 ± 1.5	<0.0001
Duration until disappearance of HBsAg (month)	6.7 ± 8.5	3.4 ± 6.5	<0.0001
Persistence of HBsAg positivity more than 6 months	25 (23.4)	9 (8.6)	0.003
Persistence of HBsAg positivity more than 12 months	8 (7.5)	1† (0.9)	0.018
Sexual transmission	81/84 (96.4)‡	71/79 (89.9)§	0.095
Treatment with NAs	61 (57.0)	42 (40.0)	0.013

Data are presented as n (%), mean ± standard deviation. HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; ALT, alanine aminotransferase; NAs, nucleotide analogs.

*Non-A genotypes include genotypes B, C, D, F and H (n = 25, 77, 1, 1, and 1, respectively).

†One patient had genotype C.

‡Transmission routes were unknown for 23 patients.

§Transmission routes were unknown for 26 patients.

Helsinki and was approved by the Ethics Committees of the institutions involved. Every patient gave informed consent for this study.

Serological Markers of HBV Infection. HBsAg, HBeAg, antibodies to HBsAg (anti-HBs), HBeAg (anti-HBe), and HBcAg, and anti-HBc of the IgM class were tested by a chemiluminescent enzyme immunoassay (CLIA) by ARCHITECT (Abbott Japan, Tokyo, Japan). HBV DNA measurements were performed using a real-time polymerase chain reaction (PCR) assay (Cobas TaqMan HBV Auto; Roche Diagnostics, Tokyo, Japan).

Genotyping of HBV. The six major HBV genotypes (A through F) were determined serologically by enzyme immunoassay (EIA) using commercial kits (HBV GENOTYPE EIA; Institute of Immunology, Tokyo, Japan). This method is based on the pattern of detection by monoclonal antibodies of a combination of epitopes on preS2-region products, which is specific for each genotype.[17,18] Samples for which EIA could not determine the genotype were examined by direct sequencing of the pre-S2/S gene, followed by phylogenetic analysis.

Treatment With NAs. Treatments with NAs were performed using lamivudine or entecavir for more than 3 months. The individual clinicians determined if NAs were administered to patients, and when the treatment was to be started. The time to onset of treatment with NAs was measured in days from onset of AHB.

Statistical Analysis. Categorical variables were compared between groups by the chi-squared test and noncategorical variables by the Mann-Whitney *U* test. A *P* value less than 0.05 was considered significant. Multivariate analysis was performed using a backward stepwise logistic regression model to determine independent factors for viral persistence following AHB. Variables in the multivariate analysis were selected based on variables that were marginally significant with $P < 0.1$ in univariate analysis. Maintenance of HBsAg positivity was analyzed using the Kaplan-Meier method and significance was tested with the log-rank test. STATA Software (StataCorp, College Station, TX) v. 11.0 was used for analyses.

Results

Comparison of Characteristics Between Genotype A and Non-A Genotype AHB Patients. A total of 107 AHB patients (50.5%) were infected with genotype A while 105 AHB patients (49.5%) were infected with non-A genotypes, including genotypes B (25 [11.8%]), C (76 [35.8%]), D (1 [0.5%]), F (1 [0.5%]), and H (1 [0.5%]). Compared to those infected with non-A genotypes, genotype A patients were significantly younger (36.3 ± 12.0 versus 40.7 ± 14.3 years, $P = 0.032$), predominantly men (95.3% versus 71.4%, $P < 0.001$), and more frequently positive for HBeAg (97.2% versus 75.2%, $P < 0.001$). Moreover, genotype A patients had a lower peak ALT levels (1,210 ± 646 versus 2,225 ± 2,851 IU/L, $P = 0.045$) and a higher peak level of HBV DNA (6.7 ± 8.5 versus 3.4 ± 6.5 log copies/mL, $P < 0.0001$). A significantly higher percentage of genotype A patients were treated with NAs (57% versus 40%, $P = 0.013$). These data are summarized in Table 1.

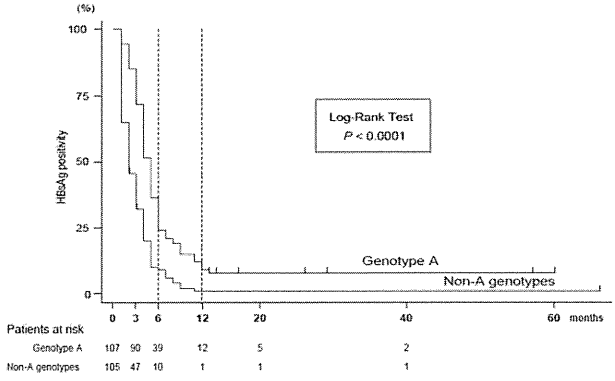

Fig. 1. Comparison of the cumulative proportion of AHB patients maintaining HBsAg positivity between genotype A and non-A genotypes, analyzed using the Kaplan-Meier test. $P < 0.0001$, genotype A: red line, non-A genotypes: blue line.

Cumulative Maintenance of HBsAg Positivity During Follow-up in Patients With Genotype A and Non-A Genotypes. In the patients infected with genotype A and non-A genotypes, the mean durations of HBsAg positivity maintenance were 6.7 ± 8.5 and 3.4 ± 6.5 months, respectively ($P < 0.0001$; Table 1, Fig. 1). For 6 months after AHB onset, the number of patients with genotype A and non-A genotypes maintaining HBsAg positivity were 39/107 (36.4%) and 10/105 (9.5%), respectively ($P < 0.001$). However, in many patients HBsAg disappeared between 7 and 12 months after AHB onset; that is, HBsAg disappeared in 31/107 (29.0%) of patients with genotype A and in 9/105 (8.6%) of patients with non-A genotypes during this time period. However, in some patients HBsAg never disappeared after persisting for more than 12 months following AHB onset. When chronicity after AHB was defined as the persistence of HBsAg for more than 12 months, chronicity developed in 7.5% (8/107) of patients with genotype A and in 0.9% (1/105) of patients with non-A genotypes ($P = 0.018$).

Comparison of Characteristics Between Patients in Whom HBsAg Persisted More Than 6 or 12 Months and Those With Self-Limited AHB Infection. Table 2 compares the demographic and clinical characteristics between patients in whom HBsAg disappeared within 6 months and those in whom HBsAg persisted for more than 6 months from AHB. The peak ALT levels ($1{,}882 \pm 2{,}331$ versus $1{,}018 \pm 696$ IU/L, $P = 0.0024$) and peak HBV DNA levels (6.3 ± 1.6 versus 7.4 ± 1.6 mg/dL, $P = 0.0004$) were significantly higher and lower in the former group than in the latter group, respectively. Moreover, marked differences were present in the distribution of genotypes between the two groups. The percentage of the HBV genotype A (46.1% versus 73.5%, $P = 0.003$) was significantly higher among patients in whom HBsAg was persistent for more than 6 months. In addition, we compared the demographic and clinical characteristics between patients in whom HBsAg disappeared within 12 months and those in whom HBsAg persisted for more than 12 months from AHB. Peak ALT ($1{,}787 \pm 2{,}118$ versus 775 ± 513 IU/L, $P = 0.0089$) and peak total bilirubin (8.7 ± 8.2 versus 3.8 ± 6.6 mg/dL, $P = 0.0039$) levels were significantly higher in the former group than in the latter group. In contrast, the peak HBV DNA levels (6.4 ± 1.6 versus 7.9 ± 1.4 mg/dL, $P = 0.0046$) were significantly lower

Table 2. Comparison Between Patients With Chronicity Following Acute Hepatitis B and Those With Self-Limited Acute Infections Determined by the Persistence of HBsAg for More Than 6 or 12 Months

Features	Disappearance of HBsAg Within 6 Months (n = 178)	Persistence of HBsAg for More Than 6 Months From AHB (n = 34)	*P* Value	Disappearance of HBsAg Within 12 Months (n = 203)	persistence of HBsAg for More Than 12 Months From AHB (n = 9)	*P* Value
Age (years)	38.2 ± 13.1	40.0 ± 14.5	0.454	38.1 ± 13.2	46.7 ± 14.0	0.061
Male sex	147 (82.6)	30 (88.2)	0.416	169 (83.3)	8 (88.9)	0.677
HBeAg positive	150 (84.3)	32 (94.1)	0.131	175 (86.2)	8 (88.9)	0.815
ALT (IU/L)	1882 ± 2331	1018 ± 696	0.0024	1787 ± 2118	775 ± 513	0.0089
Total bilirubin (mg/dL)	8.6 ± 7.5	8.7 ± 11.3	0.137	8.7 ± 8.2	3.8 ± 6.6	0.0039
HBV DNA (log copies/mL)	6.3 ± 1.6	7.4 ± 1.6	0.0004	6.4 ± 1.6	7.9 ± 1.4	0.0046
HBV genotype						
Non-A	96 (53.9)	9 (26.5)		104 (51.2)	1 (11.1)	
A	82 (46.1)	25 (73.5)	0.003	99 (48.8)	8 (88.9)	0.018
Sexual transmission	128/137 (93.4)*	24/26 (92.3)†	0.711	146/157 (93.0)‡	6/6 (100.0)§	0.356
NAs treatment (+)	82 (46.1)	21 (61.8)	0.093	98 (48.3)	8 (88.9)	0.017

Data are presented as n (%) and mean ± SD. HBsAg, hepatitis B surface antigen; AHB, acute hepatitis B, HBeAg, hepatitis B e-antigen; ALT, alanine aminotransferase; HBV, hepatitis B virus; NAs, nucleotide analogs.

*Transmission routes of 41 patients were unknown.

†Transmission routes of 8 patients were unknown.

‡Transmission routes of 46 patients were unknown.

§Transmission routes of 3 patients were unknown.

Table 3. Multivariate Analysis of Factors Independently Associated With Persistence of HBsAg Positivity Following Acute Hepatitis B

	Persistence of HBsAg More Than 6 Months From AHB		
Factors	Odds Ratio	95% CI	*P* Value
ALT (per 1 IU/L increase)	1.000	0.999-1.000	0.035
HBV DNA (per 1 log copy/mL increase)	1.176	0.931-1.484	0.173
Genotypes			
Non-A	1.00		
A	4.224	1.853-9.631	0.001

95% CI, 95% confidence interval; ALT, alanine aminotransferase; HBV, hepatitis B virus.

in the former group than in the latter group. The percentages of HBV genotype A (48.8% versus 88.9%, $P = 0.018$) and NAs treatment (+) (48.3% versus 88.9%, $P = 0.017$) were significantly higher among patients in whom the HBsAg persisted for more than 12 months.

Factors Independently Associated With Viral Persistence Following AHB. A stepwise logistic regression model was used to perform multivariate analysis which explains relationships between some factors and persistence of HBsAg positivity more than 6 months following AHB. Peak ALT level, peak HBV DNA level, genotype A, and treatment with NAs were retained in the final multivariate logistic model in a backward stepwise manner ($P < 0.1$). For predicting the persistence of HBsAg for more than 6 months, only genotype A was independently associated with progression of AHB to the persistence of HBsAg (odds ratio [OR]: 4.224, $P = 0.001$, Table 3).

Characteristics of Patients Who Progressed to Chronicity That Was Defined as the Persistence of HBsAg for More Than 12 Months Following Acute Hepatitis B. Table 4 shows the clinical and virological characteristics of nine patients who progressed to chronicity defined as the persistence of HBsAg for more than 12 months following AHB. Among the nine patients who progressed to chronicity from AHB, eight (88.9%) were men and eight (88.9%) were HBeAg-positive. In general, among the patients who progressed to chronicity following AHB, the peak HBV DNA levels were high, and the peak total bilirubin and ALT levels were low. In eight (88.9%) patients, entecavir was administered; however, the duration until the onset of NA treatment from AHB onset was long (75-570 days).

Early Onset of Treatment With NAs Was Able to Prevent Viral Persistence After AHB Caused by Genotype A. The cumulative proportion maintaining HBsAg positivity during follow-up, expressed in terms of time after AHB onset, were significantly longer in patients with NAs treatment than in those without NAs treatment ($P = 0.046$, Fig. 2A). Table 5 shows the percentages of patients in whom HBsAg persisted for more than 6 or 12 months among patients categorized based on the period of time (i.e., duration) until the onset of NAs treatment. For patients in whom the onset of NAs treatment was less than 4 weeks from the onset of AHB, 12.7% of the patients showed persistent HBsAg for more than 6 months, while none showed HBsAg positivity for more than 12 months. For patients in whom the onset of NAs treatment was at 5-8 weeks, 37.5% of the patients showed persistent HBsAg for more than 6 months, whereas none showed persistent HBsAg for more than 12 months. For all groups, the period of HBsAg positivity in patients starting NAs treatment within 8 weeks from AHB onset was significantly shorter than that in patients beginning NAs treatment after more than 8 weeks from AHB onset ($P < 0.0001$, Fig. 2B). Patients starting NAs treatment within 8 weeks from AHB onset never progressed to chronicity after AHB caused by genotype A.

Table 4. Characteristics of Patients Who Progressed to Chronicity Following Acute Hepatitis B

Case	Age	Gender	HIV	HBeAg	HBV DNA (log copies/mL)	Total Bilirubin (mg/dL)	ALT (IU/L)	Observation Period (Months)	NAs Treatment	Duration Until NAs Treatment (Days)	Transmission Routes	Genotype
1	23	Male	(−)	(+)	7.6	1.7	1271	26	ETV	570	Heterosexual	A
2	40	Male	(−)	(−)	8.8	1.4	568	13	ETV	240	Heterosexual	A
3	45	Male	(−)	(+)	7.7	0.9	867	57	ETV	135	Heterosexual	A
4	37	Male	(−)	(+)	7.6	3.4	384	29	ETV	75	Unknown	A
5	54	Male	(−)	(+)	9	2	455	17	ETV	155	Homosexual	A
6	45	Male	(−)	(+)	4.8	21.2	512	60	(−)	(−)	Homosexual	A
7	61	Male	(−)	(+)	9.1	1.5	804	17	ETV	88	Unknown	A
8	56	Male	(−)	(+)	9.0	1.1	1820	14	ETV	118	Unknown	A
9	31	Female	(−)	(+)	7.4	0.8	296	66	ETV	150	Blood transfusion	C

HIV, human immunodeficiency virus; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; NAs, nucleotide analogs; ETV, entecavir.

Table 5. Proportion of Patients in Whom HBsAg Persisted for More Than 6 or 12 Months Among Patients Categorized Based on the Number of Weeks Until the Onset of NAs Treatment

Duration Until Onset of NAs Treatment (Weeks)	Persistence of HBsAg for More Than 6 Months	Persistence of HBsAg for More Than 12 Months	Total Patients
<4 weeks (n, %)	9 (12.7)	0 (0)	71
5-8 weeks (n, %)	6 (37.5)	0 (0)	16
9-12 weeks (n, %)	1 (33.3)	1 (33.3)	3
13-16 weeks (n, %)	4 (100)	1 (25.0)	4
>17 weeks (n, %)	9 (100)	6 (66.7)	9
Total	29	8	103

HBsAg, hepatitis B surface antigen; NAs, nucleotide analogs.

Discussion

A multicenter nationwide study was conducted throughout Japan to evaluate the influence of clinical and virological factors on chronic outcomes in Japanese patients who contracted AHB in adulthood. The study was feasible in Japan, where a universal vaccination program for HBV has not been implemented because of the extremely high efficacy of the immunoprophylaxis that is given to babies born to carrier mothers. The implementation of this program has resulted in a decrease in the persistent HBV carrier rate from 1.4% to 0.3%.[19] Selective vaccination means that Japanese are more likely to be infected with HBV by way of horizontal transmission since the percentage of the population possessing anti-HBs is much lower than that in countries in which universal vaccination programs have been established.[20] In addition, Japan is faced with the ever-increasing impacts of globalization: as many as 17 million Japanese travel abroad and over 7 million people visit Japan from overseas each year. This "population mixing" may help to explain the increased prevalence in Japan of AHB due to genotype A, which is transmitted through indiscriminate sexual contact. Consequently, Japan may be the only country in the world where the influences of HBV genotypes, including genotype A (as is predominant in Western countries) and genotypes B and C (as are predominant in Asian countries), on chronic outcomes after AHB can be compared.

Currently, the persistence of HBsAg in serum for more than 6 months is considered to represent a progression to chronic infection.[21] However, our data showed that HBsAg frequently disappeared between 7 to 12 months after the onset of AHB in patients with genotype A (31/107 [29.0%]) and non-A genotypes (9/105 [8.6%]) (Fig. 1). These patients were considered to exhibit prolonged cases of AHB, rather than persistent infection. This finding reflects the higher sensitivity of the most up-to-date assays for HBsAg as compared with previous methods. In the present study, HBsAg was measured by CLIA, which has been reported to be about 150 times more sensitive in the detection of HBsAg than reverse passive hemagglutination (RPHA)-HBsAg, which has been used for the last 30 years in Japan.[22] The use of a more sensitive assay for HBsAg results in a longer period during which HBsAg may be detected. In this study, HBsAg did not disappear in nine patients after remaining continuously detectable for more than 12 months. Therefore, the persistence of HBsAg for more than 12 months, as measured with a highly sensitive method for detecting HBsAg, may be suitable for defining the progression of AHB to chronicity; however, further study is necessary to determine whether this definition is appropriate worldwide.

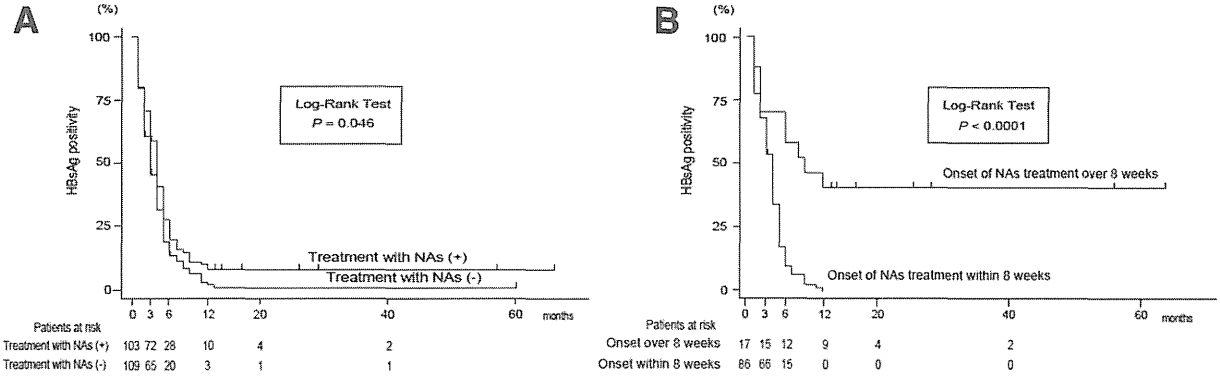

Fig. 2. (A) Comparison of the cumulative proportion of AHB patients maintaining HBsAg positivity between treatment with NAs (+) and treatment with NAs (−), as analyzed using the Kaplan-Meier test. $P = 0.046$, treatment with NAs (+): red line, treatment with NAs (−): blue line. (B) Comparison of the cumulative proportion of AHB patients in genotype A maintaining HBsAg positivity between treatment onset with NAs within 8 weeks and treatment onset with NAs over 8 weeks after onset of AHB, as analyzed using the Kaplan-Meier test. $P < 0.0001$, treatment onset with NAs over 8 weeks: red line, treatment onset with NAs within 8 weeks: blue line.

It has been reported that ~10% of patients who contract HBV as adults do not clear HBsAg from their serum and become carriers.[23] Meanwhile, a wide variation has been seen in the rate of persistence after AHB infection in adults. For example, viral persistence following AHB was seen in 0.2% (1/507) of adults in Greece,[24] 7.7% (5/65) of adult Alaskan Eskimos, and 12.1% (7/58) of adults in Germany.[25] The difference in the proportion of patients progressing from AHB to chronicity in different regions may be attributable to virological and host factors. In this study, 4.2% (9/212) of patients progressed to chronicity after AHB: 7.5% (8/107) of those infected with genotype A and 0.9% (1/105) of those infected with non-A genotypes. The non-A genotypes included genotypes B, C, D, F, and H (n = 25, 77, 1, 1, and 1, respectively). Genotypes B and C are predominant in eastern Asian countries, where the majority of those infected with HBV acquired the virus during the perinatal period by way of vertical transmission.[26] On the other hand, genotype A is predominant in Western countries, where the main route is horizontal transmission later in life.[26,27] Because HBeAg persists long after the infection in the genotype C as compared to other genotypes, this genotype has been shown to be a risk factor for perinatal and horizontal transmission in newborns and children.[28] The predominance of genotype A in Western countries may be attributable to a higher chronicity rate following AHB by way of horizontal transmission in adults.

In this study the characteristics of AHB associated with genotype A were a higher peak level of HBV DNA and a lower peak level of ALT. These findings were similar to those for patients with HBV-HIV coinfection.[29] Such characteristics of genotype A or coinfection with HIV are assumed to be attributable to milder hepatitis associated with weaker cellular immune responses. More slowly replicating viruses have been reported to evoke weaker cellular responses, enhancing the likelihood of persistence.[30] Indeed, our prior study showed that the replication of genotype A was significantly slower than that of genotype C in immunodeficient, human hepatocyte chimeric mice.[31] Moreover, variation among genotypes in the expression pattern of HBeAg may affect the progression of AHB to chronicity. Another previous study of ours revealed that a single form of HBeAg was detected by western blot analysis in serum samples from patients infected with genotypes B through D, but that two additional larger forms of HBeAg were detected in patients with genotype A.[32] Milich and Liang[33] reported that HBeAg may modulate the host immune response as a tolerogen to promote chronicity. Therefore, the different expression pattern of HBeAg by genotype A HBV may contribute to chronicity following AHB.

Early NAs initiation appeared to enhance the viral clearance across genotypes, although treatment with NAs did not show any overall benefit in duration of HBsAg. Previous studies examining the efficacies of NAs for preventing progression to chronic infection after AHB have reported conflicting results. Some small-scale studies have suggested the efficacy of lamivudine and entecavir in preventing the progression of AHB to chronic hepatitis.[34,35] Another study showed a lower seroconversion rate of HBsAg in lamivudine users.[36] Further, a randomized placebo-controlled trial showed no significant difference in clinical outcomes.[37] However, these previous studies did not mention the prevalence of HBV genotypes in the respective study populations. Although this was a retrospective study, our study included data on the prevalence of HBV genotypes. Additionally, our findings suggested that larger prospective randomized studies for every HBV genotype should be performed to determine whether early treatment with NAs prevented the progression of AHB to a chronic state.

In conclusion, in Japan genotype A was an independent risk factor for progression to chronic infection following AHB in adults. Confirmation of this association in patients with AHB in other countries is desirable and may provide insight into the pathogenetic mechanisms underlying this association. Early NA treatment appeared to reduce the likelihood of chronicity but this potentially important intervention needs to be prospectively studied before recommendations can be made.

Appendix

Members of the Japanese AHB Study Group include Yasuharu Imai (Ikeda Municipal Hospital), Norie Yamada, Hideaki Takahashi (St. Marianna University School of Medicine), Koji Ishii (Toho University School of Medicine), Hideyuki Nomura (Shin-Kokura Hospital), Jiro Nishida (Tokyo Dental Collage Ichikawa General Hospital), Shigeru Mikami (Kikkoman Hospital), Tsuneo Kitamura (Juntendo University Urayasu Hospital), Akihito Tsubota (Kashiwa Hospital Jikei University School of Medicine), Noritomo Shimada (Shinmatsudo Central General Hospital), Tetsuya Ishikawa (Nagoya University Graduate School of Medicine), Yoshiyuki Ueno (Tohoku University Graduate School of Medicine), Tomoyoshi Ohno (Social Insurance Chukyo Hospital), Etsuro Orito (Nagoya

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The relationship between physical signs of aging and social functioning in persons with Down syndrome in Japan

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Background: In Japan, there have been no substantial studies of social function and physical aging in adults with Down syndrome. The aim of the present study was to examine social functions (movement, conversation, and daily living skills) and physical signs of aging in adults with Down syndrome in Japan, and to analyze the relationship between changes in social function and age.

Methods: A cross-sectional survey of persons with Down syndrome who were 15 years of age or older (15-65 years old) was conducted. The survey was conducted in patients associations, institutes, group homes, and workplaces from July to December 2009. Primary caregivers, such as family members and institute staff, were asked to complete a questionnaire on the subjects' living situation, movement ability, conversational skills, daily living skills, and 10 characteristics of physical aging at the time of the survey.

Results: The total number of subjects was 315. Subjects' movement ability, conversational ability, and daily living skills declined as a function of age. Canities (40.6%) were the most prevalent physical sign of aging, followed by missing teeth, hump back, and skin wrinkling. Further, physical aging was related to a decline in social functions ($p < 0.001$).

Conclusion: The present study showed that adults with Down syndrome exhibit signs of physical aging earlier than do the general population, and that physical aging is associated with social functioning. Thus, the appearance of physical aging might indicate a decline in social functioning.

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Key words: Down syndrome, aging, movement, conversation, daily living skills, physical signs of aging

Introduction

The life expectancy for individuals with Down syndrome has been extended: while it was approximately 12 years in 1949, it was reported 60 years in 2002,[1,2] and in a survey in Japan, approximately 50 years.[3] This increase in life expectancy has led to an escalation in research focused on health problems in adults with Down syndrome[4,5,6] and the quality of life of their family members.[7,8]

There have also been a number of reports addressing factors related to social adaptability such as age-related changes in movement, language ability, and daily living skills. Regarding movement, it has been noted that persons with Down syndrome have delayed motor skill development in childhood relative to healthy children;[9,10] that they develop a characteristic manner of walking to compensate for lower

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muscle tone;[11] and that their movements are slower than those of healthy children.[12, 13]

In one study on conversational ability in persons with Down syndrome, of the 374 participants (aged 14 to 62), 41.6% were able to understand the conversation without difficulty, and 15.2% were able to use words without difficulty.[14] Additionally, in a survey comparing 55 persons with Down syndrome (aged 30 to 59) and 75 persons with other intellectual disabilities (aged 30 to 69), persons with Down syndrome exhibited lower conversational fluency across all ages.[15]

Daily living skills were not found to be appreciably impacted by age in one study,[16] but Bertoli et al.[14] reported that the proportion of persons with Down syndrome that exhibited functional decline increased rapidly after age 30. Esbensen et al.[17] stated that although the severity of intellectual disability determined the level of assistance Down syndrome patients required for daily living activities, even some individuals with mild or moderate disability were in a self-supporting category.

Adults with Down syndrome have a greater incidence of premature cataracts than the general population.[18,19] Regarding oral health, adults with Down syndrome have been shown to have fewer caries[20,21] but a greater incidence of severe periodontal disease[22] than do the general population. Some studies have suggested that alopecia totality or universality[23] and skin wrinkling are more prevalent in individuals with Down syndrome[24].

Because there is no system of patient registration for persons with Down syndrome in Japan, placement and social function in the Down syndrome population have not been investigated. However, there has been some recent investigation into early-onset dementia[25,26] and the consequent problems of life support system[2,8,16] for adults with Down syndrome. Generally, persons with Down syndrome show early-onset physical aging, but there are few reports about the overall physical signs of aging. The present study therefore examines the status of social function (movement, conversation, and daily living skills) and the characteristics of physical aging in persons with Down syndrome aged 15 and older in Japan, and analyzes the change in these variables as a function of age.

Materials and methods

Research subjects

The present study is a cross-sectional study of social adaptability among persons with Down syndrome aged 15 years and older (15-65 years old). Placements considered for persons with Down syndrome were at home, in an institute such as a welfare facility for the intellectually or physically disabled (hereafter referred to as simply, "institutes"), and in a group home (GH). Institutes and GHs were surveyed on the number of subjects accommodated, and were asked for written cooperation. For research cooperation, two groups of patient association and a total of 127 places including institutes, workplaces, and GHs accepted in their reply, and a total of 1,300 copies of the survey were distributed. The survey was carried out from July to December in 2009.The survey was conducted with the approval of the Nagasaki University Graduate School of Biomedical Sciences Ethics Committee. In implementing the survey, an emphasis was placed on protecting privacy.

Questionnaire

A questionnaire was administered that assessed subjects' social functions (movement, conversation, and daily living skills; 3 items), physical signs of aging (ten items), disease prevalence (9 items), and mental status (36 items). Subjects were additionally asked about the attributes of age, sex, and placement (choices included living at home with family, a GH, or an institute). Social function was assessed on a three-point scale, and replies for diseases and signs were indicated by a "yes" or "no."

The criteria for movement were as follows: (1) independent group (able to run, able to walk alone), (2) assistance group (able to walk with assistance), and (3) difficulty group (able to move by crawling, unable to move independently).

The criteria we used to assign participants according to conversation were as follows: (1) independent group (conversation is clear, able to converse normally), (2) assistance group (able to converse in familiar situations), and (3) difficulty group (able to convey meaning using a single word, conversation is difficult).

The criteria for daily living skills were as follows: (1) independent group (independent), (2) assistance group (able to live independently if prompted, sometimes needs assistance), and (3) difficulty group (always needs assistance, incapable of living alone).

The ten physical signs of aging assessed were as follows: (1) long eyebrows, (2) alopecia, (3) canities, (4) missing teeth, (5) humpback, (6) cataracts, (7) flabby skin under the eyes, (8) longitudinal groove along nails, (9) senile freckles, and (10) skin wrinkling.

Persons familiar with the daily lives of the subjects who lived with subjects and caregivers who provided daily support for subjects at institutes and GHs were asked to com-

plete this survey. To facilitate compliance, care was taken to make the three-point scales of the criteria as comprehensible as possible.

Statistical analysis

The function and physical signs of aging was compared between age groups by using χ^2 test. The simultaneous effects of age and the number of physical signs of aging on social function were analyzed by multiple linear regression models. All statistical analyses were performed by using SPSS Ver.18. A p-value of less than 0.05 was considered to be statistically significant.

Results

At 551 responses to the survey, the response rate was 42.4%. Incomplete responses, with missing values of sex, age or physical signs of aging were excluded. Remaing 315 responses for analysis.

Results showed that 39% of respondents were family members (parents and siblings), 55% were facility caregivers, and 6% were unknown. The mean age of subjects in various placements living at home was 24.7 years (15–45 years, SD = 7.2); the mean age of subjects living in a GH was 38.4 years (19–59 years, SD = 10.3); and the mean age of subjects living in an institute was 42.3 years (15–65 years, SD = 11.4). Thus, results indicate that, as age increases, there is a significant reduction in the proportion of persons living at home, along with an increase in the proportion of persons living in an institute (Cochran-Armitage test, $p < 0.01$).

Table 1 shows the breakdown of sex and social functions for Down syndrome subjects of different ages. The mean age of the subjects was 33.22 years (15–65 years, SD = 12.8), with the minimum at 15 years and the maximum at 65 years. Regarding sex, 166 (52.7%) were men and 149 (47.3%) were women, and no significant difference in the sex ratio between various age groups was found. The majority of subjects could move without assistance until 40s: 298 (94.5%) of the subjects were in the independent group. In three items

Table 1. Gender, Social Function and Age of Individuals with Down syndrome

		Age	15-19	20-29	30-39	40-49	50-59	60-	P[a]
	n (%)	Mean years (SD;Range)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender									
Male	166 (52.7)	33.64 (13.2;15-63)	22 (55.0)	56 (52.3)	36 (47.4)	27 (54.0)	20 (60.6)	5 (55.6)	0.870
Female	149 (47.3)	32.75 (12.4;15-65)	18 (45.0)	51 (47.7)	40 (52.6)	23 (46.0)	13 (39.4)	4 (44.4)	
Movement									
Independence	298 (94.6)		40 (100)	107 (100)	72 (94.7)	47 (94.0)	26 (78.8)	6 (66.7)	
Assistance	15 (4.8)		0 (0)	0 (0)	4 (5.3)	3 (6.0)	6 (18.2)	2 (22.2)	p<0.001
Difficulty	2 (0.6)		0 (0)	0 (0)	0 (0)	0 (0)	1 (3.0)	1 (11.1)	
Conversation									
Independence	120 (38.1)		21 (52.5)	50 (46.7)	27 (35.5)	15 (30.0)	4 (12.1)	3 (33.3)	
Assistance	85 (27.0)		9 (22.5)	34 (31.8)	23 (30.3)	11 (22.0)	6 (18.2)	2 (22.2)	p<0.001
Difficulty	110 (34.9)		10 (25.0)	23 (21.5)	26 (34.2)	24 (48.0)	23 (69.7)	4 (44.4)	
Daily living skills									
Independence	61 (19.4)		11 (27.5)	32 (29.9)	9 (11.8)	7 (14.0)	2 (6.1)	0 (0)	
Assistance	179 (56.8)		27 (67.5)	62 (57.9)	48 (63.2)	25 (50.0)	14 (42.4)	3 (33.3)	p<0.001
Difficulty	75 (23.8)		2 (5.0)	13 (12.2)	19 (25.0)	18 (36.0)	17 (51.5)	6 (66.7)	
Total	315 (100)	33.22 (12.8;15-65)	40 (12.7)	107 (34.0)	76 (24.1)	50 (15.9)	33 (10.5)	9 (2.9)	

[a] Cochran-Armitage test ; SD, Standard deviation

of social function ,the overall distribution of subjects number who were in assistance and difficulty group increased and independence group decreased with age. Thus, results indicate movement, conversational ability, and daily living skill significantly decline with age (Cochran-Armitage test, $p < 0.01$).

Table 2 shows the frequency of the physical signs of aging for different ages of subjects with Down syndrome. The frequency of all 10 items significantly increased with age (Cochran-Armitage test, $p < 0.01$). Canities were most prevalent, reported by 40.6%. For all physical signs of aging except long eyebrows and alopecia, the proportion of participants was over 20%.

Table 3 shows the results of multiple regression analysis between the independent variables (age and the number of physical signs of aging) and the dependent variable (social function). The relationships of movement, daily living skills, and the number of physical signs of aging, with age were statistically significant. Movement was related with to the number of physical signs of aging ($p < 0.001$) and age ($p = 0.029$). Similarly, daily living skills were related to the number of physical signs of aging ($p < 0.001$) and age ($p = 0.032$). In contrast, conversational ability was related to the number of physical signs of aging ($p < 0.001$), but was not related to age ($p = 0.434$).

Table 2. Sings of Aging and Age of Individuals with Down syndrome

Physical signs of aging		Age	total	15-19	20-29	30-39	40-49	50-59	60-	P[a]
		n	315	40	107	76	50	33	9	
Long eyebrow	+	n	39	0	5	10	5	16	3	p<0.001
		(%)	(12.4)	(0)	(4.7)	(13.2)	(10.0)	(48.5)	(33.3)	
	–	n	276	40	102	66	45	17	6	
		(%)	(87.6)	(100)	(95.3)	(86.8)	(90.0)	(51.5)	(66.6)	
Alopecia	+	n	48	0	6	17	7	11	7	p<0.001
		(%)	(15.2)	(0)	(5.6)	(22.4)	(14.0)	(33.3)	(77.8)	
	–	n	267	40	101	59	43	22	2	
		(%)	(84.8)	(100)	(94.4)	(77.6)	(86.0)	(66.7)	(22.2)	
Canities	+	n	128	6	23	32	31	27	9	p<0.001
		(%)	(40.6)	(15.0)	(21.5)	(42.1)	(62.0)	(81.8)	(100)	
	–	n	187	34	84	44	19	6	0	
		(%)	(59.4)	(85.0)	(78.5)	(57.9)	(38.0)	(18.2)	(0)	
Missing teeth	+	n	81	0	4	19	24	26	8	p<0.001
		(%)	(25.7)	(0)	(3.7)	(25.0)	(48.0)	(78.8)	(88.9)	
	–	n	234	40	103	57	26	7	1	
		(%)	(74.3)	(100)	(96.3)	(75.0)	(52.0)	(21.2)	(11.1)	
Hump back	+	n	89	6	19	26	17	14	7	p<0.001
		(%)	(28.3)	(15.0)	(17.8)	(34.2)	(34.0)	(42.4)	(77.8)	
	–	n	226	34	88	50	33	19	2	
		(%)	(71.7)	(85.0)	(82.2)	(65.8)	(66.0)	(57.6)	(22.2)	
Cataracts	+	n	71	4	15	14	14	18	6	p<0.001
		(%)	(22.5)	(10.0)	(14.0)	(18.4)	(28.0)	(54.5)	(66.7)	
	–	n	244	36	92	62	36	15	3	
		(%)	(77.5)	(90.0)	(86.0)	(81.6)	(72.0)	(45.5)	(33.3)	
Flabby skin under the eyes	+	n	69	2	7	19	12	22	7	p<0.001
		(%)	(21.9)	(5.0)	(6.5)	(25.0)	(24.0)	(66.7)	(77.8)	
	–	n	246	38	100	57	38	11	2	
		(%)	(78.1)	(95.0)	(93.5)	(75.0)	(76.0)	(33.3)	(22.2)	
Longitudinal groove along nails	+	n	65	0	7	18	12	20	8	p<0.001
		(%)	(20.6)	(0)	(6.5)	(23.7)	(24.0)	(60.6)	(88.9)	
	–	n	250	40	100	58	38	13	1	
		(%)	(79.4)	(100)	(93.5)	(76.3)	(76.0)	(39.4)	(11.1)	
Senile freckles	+	n	63	3	3	17	15	20	5	p<0.001
		(%)	(20.0)	(7.5)	(2.8)	(22.4)	(30.0)	(60.6)	(55.6)	
	–	n	252	37	104	59	35	13	4	
		(%)	(80.0)	(92.5)	(97.2)	(77.6)	(70.0)	(39.4)	(44.4)	
Skin wrinkling	+	n	90	0	5	24	22	30	9	p<0.001
		(%)	(28.6)	(0)	(4.7)	(31.6)	(44.0)	(90.9)	(100)	
	–	n	225	40	102	52	28	3	0	
		(%)	(71.4)	(100)	(95.3)	(68.4)	(56.0)	(9.1)	(0)	

[a] Cochran-Armitage test

Table 3. Multiple regression analysis for Social Function with Age and Number of Physical Signs of Aging as Independend variable

Dependent variable	Independent variable	B	SE	P
Movement	Number of Physical signs of aging	0.023	0.007	0.001
	Age	0.032	0.015	0.029
Conversation	Number of Physical signs of aging	0.106	0.022	p<0.001
	Age	0.037	0.047	0.434
Daily living skills	Number of Physical signs of aging	0.079	0.016	p<0.001
	Age	0.075	0.035	0.032

B, Regression coefficient ; SE, Standard Error

Discussion

This study showed that social function declined with age and physical signs of aging increased with age. Conversational ability and daily living skills began declining in Down syndrome patients at a relatively young age, however, movement ability remained stable until approximately age 50 in the present study. The results of a previous study that assessed walking ability in persons with Down syndrome[13] showed a significant decline in both walking speed and distance in an older group (aged 55–61) compared with a younger group (aged 41–46). The present study supports the results this study, with walking ability being comparatively maintained.

Carr[25,27,28] reported that persons with Down syndrome aged 9–45 have relatively stable language ability in his longitudinal study. It has, however, also been reported that language ability also declined significantly as age increases[28]. The present study showed that conversation declined significantly as aging. The difference to the research results by Carr presumably included the difference in assessment scale, subjects, and the social background.

Longitudinal studies[27,28] that analyzed the daily living skills of Down syndrome patients over time found that daily living skills peak at age 30 and thereafter decline slowly.[25] Furthermore, a cross-sectional study[14] showed that the proportion of individuals who exhibited a functional decline in daily living skills increased at age 30 and beyond. Despite slight differences in the peaking ages, the present results appear to be relatively consistent with previous results in that there was a gradual decline following age 30.

It is known that persons with Down syndrome may age prematurely and display signs of aging as early as 30–40 years of age.[13] In the present study, the frequency of 10 physical signs of aging were assessed. Canities, missing teeth, humpback, and skin wrinkling were the most prevalent (>25%) physical signs of aging found in the present study. It has been previously observed that Down syndrome patients have fewer teeth[20] and a greater frequency of missing teeth than the general population.[22] Additionally, the present study demonstrated an increase in missing teeth with advancing age (30–39 years, 25.0%; 40–49 years, 48.0%; 50–59 years, 78.8%). It has been stated that adults with Down syndrome have a lower incidence of caries[20,21] but a greater incidence of severe periodontal disease[22] than do the general population. Therefore, it is possible that periodontal disease is the cause of the increased prevalence of missing teeth in people with Down syndrome. However, these reports did not include data on the frequency of missing teeth, because the number of subjects was low.

In one report,[24] skin wrinkling of the forearm and periorbital region increased with age in persons with Down syndrome, and the frequency of this was greater than in the general population. Our results are in general consistent with prior research: the frequency of skin wrinkling and that frequency of flabby skin under the eye increased dramatically aged 40–49 to 50–59.

Social functions, movement ability, and daily living skills were related to the number of physical signs of aging and age. This suggests that physical aging and the decline in movement ability appear simultaneously. However, conversational ability was associated with physical aging, but not age. Therefore, when physical changes appear in young adults with Down syndrome, these individuals should be screened for deficits in conversational ability.

A limitation of the present study is that the subject pool was limited to individuals with social connections, meaning that our results cannot generalize to persons without social support. If caregivers are aware that the appearance of physical changes and a decline in social function may co-occur, adults with Down syndrome might receive greater daily living support and a better quality of life. A longitudinal study on the relationship between changes in social function and physical aging in adults with Down syndrome should be conducted in the future.

Conclusion

The present study provides important suggestion regarding the natural course of a decline in adults with Down syndrome in Japan. The present study showed that adults with Down syndrome exhibit age-related declines in social functions, and show signs of physical aging earlier than does the general population. Furthermore, the number of physical signs of aging was associated with the decline in social function. This result suggests that the appearance of physical aging and the decline in social functions may co-occur. If caregivers are aware of this, they can lend more support upon observance of physical aging, thus improving the quality of life of people with Down syndrome.

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SPECIAL ISSUE PAPER

Pilot Study: Efficacy of Sensory Integration Therapy for Japanese Children with High-Functioning Autism Spectrum Disorder

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Abstract

This study's objective was to investigate the efficacy of sensory integration therapy (SIT) for children with high-functioning autism spectrum disorder (HFASD). The subjects were 20 HFASD children with IQs above 70 selected from previously collected data. Eight participated in individual SIT sessions, and 12 participated in group therapy (GT) including social skill training, communication training, kinetic activities, and child–parent play for 8–10 months. Changes in Total score and five Index scores on the Japanese version of the Miller Assessment for Preschoolers before and after therapy between children in the SIT and GT groups were compared. The results showed that Total score and all Index scores except for Verbal Index increased significantly in the SIT group, while only Total score increased in the GT group. Furthermore, the SIT group showed more improvement compared with the GT group in Total score and on Coordination, Non-verbal, and Complex Index scores. SIT might have a more positive effect on motor coordination abilities, non-verbal cognitive abilities, and combined abilities of sensory motor and cognition in children with HFASD when compared with GT. This study has limitations such as being an analysis of previously collected data. Further study should be conducted with a randomized control trial.

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Keywords

autism spectrum disorder; sensory integrative therapy; paediatric occupational therapy

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Introduction

Sensory integration (SI) theory was originally developed by A. Jean Ayres to focus on the neurological processing of sensory information (Ayres, 1972). Sensory integrative therapy (SIT) or SI approach has been used for the treatment of challenged children since the 1970s. Many studies have demonstrated the effectiveness of the SIT approach for challenged children (Grimwood and Rutherford, 1980; Ottenbacker, 1982; Ziviani et al., 1982; Polatajko et al., 1991; Allen and Donald, 1995; Case-smith and Bryan, 1999; Linderman and Stewart, 1999; Candler, 2003; Miller et al., 2007a, 2007b; May-Benson and Koomar, 2010).

Sensory integrative therapy has also been applied to children with autism spectrum disorders (ASD). An Internet survey questioning treatments used for children with ASD revealed that SI was the third most commonly reported intervention (Green et al., 2006). Some researchers have investigated the efficacy of SI treatment for children with ASD. For example, Miller et al. (2007a) indicated that children with ASD undergoing occupational therapy using the SI approach (OT-SI) made significant gains compared with an Activity Protocol group and a no treatment group on goal attainment scaling, the Attention subset, and the Cognitive/Social composite of the Leiter International Performance Scale—Revised. The OT-SI group improvement trends on the Short Sensory Profile, Child Behavior Checklist, and electrodermal reactivity were in the hypothesized direction. Additionally, Fazlioğlu and Baran (2008) reported that statistically significant differences in the Sensory Evaluation Form for Children with Autism scores between SIT groups and control groups indicated that SIT programmes positively affected children with autism. Pfeiffer et al. (2011) identified significant positive changes in children with ASD in a SIT group when compared with a fine motor treatment group and a significant decrease in autistic mannerisms in the SIT group. Additional studies of children with ASD or pervasive developmental disorder have provided preliminary support for SIT in areas such as reducing self-stimulating behaviours and increasing functional behaviours such as social interaction and play (Case-Smith and Bryan, 1999; Linderman and Stewart, 1999; Smith et al., 2005; Watling and Dietz, 2007). However, some studies have not affirmed the effectiveness of SIT compared with other therapy forms. A review study (Baranek, 2002) suggested that outcomes of SIT for children with autism in psychoeducational and motor categories are stronger than in other areas, at least for SI studies compared with no treatment conditions; however, effects appeared to be equal when compared with alternative treatments. Devlin et al. (2011) reported that behavioural intervention was more effective than SIT in the treatment of challenging behaviour of children with ASD. Section On Complementary And Integrative Medicine; Council on Children with Disabilities; American Academy of Pediatrics cautioned that parents should be informed that the amount of research regarding the effectiveness of SIT is limited and inconclusive (Section On Complementary And Integrative Medicine; Council on Children with Disabilities; American Academy of Pediatrics et al., 2012). Thus, although SIT has been adopted for children with ASD, its effectiveness is controversial.

Many studies demonstrated that improvements in sensory-motor skills, motor planning, and reading-related skills in children with learning disabilities, with mental retardation, or with developmental coordination disorder (DCD) were seen using SIT or SI treatment (Grimwood and Rutherford, 1980; Humphries et al., 1990; Wilson and Kaplan, 1994; Allen and Donald, 1995; Leemrijse et al., 2000; Wuang et al., 2009). However, there were no studies investigating the effectiveness of SIT for cognition, motor performance, or motor planning in children with ASD except for a single case report (Schaaf et al., 2012). Hence, an examination of the effectiveness of SIT for not only behaviour but also cognition, verbal, motor, or praxis abilities in children with ASD is warranted.

In order to clarify the effectiveness of SIT on cognition, verbal, motor, and praxis abilities on children with ASD, a comprehensive test tool is needed. The Japanese version of the Miller Assessment for Preschoolers (JMAP) (Tsuchida et al., 1989) is a standardized test that assesses cognitive abilities, verbal abilities, and sensory-motor abilities. Therefore, we expect the JMAP would be able to detect changes in the cognitive, verbal, and sensory-motor abilities in children before and after therapy. To examine the effectiveness of SIT, we compared score changes on the JMAP for individual SIT to common group therapy (GT) treatment methods by analyzing previously collected data from children with HFASD.

Thus, the purpose of this study was to examine the effectiveness of SIT on cognition, verbal, and sensory-motor abilities in children with ASD.

Method

Subjects

Subjects who satisfied the following conditions were selected from Nagasaki Prefectural Medical Treatment and Education Center's clinical records and a clinic of Nagasaki University clinical records by the first author while serving there from 1995–2011 (Table I).

(1) The subject was diagnosed with autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified by paediatricians according to DSM-IV (APA, 1994).
(2) The subject had an IQ above 70 using the Tanaka–Binet test.

Table I. Descriptive statistics for participants and period of therapy

	Group		
	Individual sensory integration	Group therapy	*p*
Number	8	12	
Male : female	8:0	10:2	ns
IQ	100.7 ± 9.6	94.8 ± 9.1	ns
Autism : Asperger	3:5	6:6	ns
Age in months at start of therapy	56.8 ± 9.0	56.3 ± 6.8	ns
Therapy duration (months)	9.3 ± 1.0	9.3 ± 0.9	ns

(3) The subjects had participated in individual SIT or GT for durations of between 8 to 10 months.

(4) The subject took the JMAP examination and completed data both before therapy and after therapy.

(5) Age at first and second testing was within the target age of JMAP, which was between 2 years and 9 months, and 6 years and 2 months.

(6) Parents gave informed consent to use data for this study during the first visit.

The basic programme at Nagasaki Prefectural Medical Treatment and Education Center was GT. However, some children could not participate in these groups because the groups were full. The first author conducted SIT in this institution to the children who could not enter GT. Some children were chosen from the clinic at Nagasaki University. These children were given SIT by the first author in a SIT room at Nagasaki University. Most of the subjects in both institutions were introduced by public health nurses or kindergarten teachers in order to provide possible therapies and to get advice for children's behaviour or communication problems. Therefore, the parents of this study's subjects did not choose institution and therapy style.

Therapy for children with autism spectrum disorder

Subjects were given either SIT (1 h) or GT (1.5 h) weekly. SIT was conducted by the first author individually. The first author is a SI therapist certified by the Japanese Sensory Integration Association. During SIT, the first author, also an occupational therapist, and a child interacted in a therapy room equipped with sensory and kinetic equipment such as a swing, ball pit, balance beam, ladder, and trampoline. The child interacted with the sensory and kinetic materials in an active, meaningful, and fun manner. Recently, the Ayres Sensory Integration Fidelity Measure (ASIFM) (Parham et al., 2011) was proposed with the following parameters: 1) Ensures physical safety; 2) Presents sensory opportunities; 3) Helps the child to attain and maintain appropriate levels of alertness; 4) Challenges postural, ocular, oral, or bilateral motor control; 5) Challenges praxis and organization of behaviour; 6) Collaborates in activity choice; 7) Tailors activity to present just-right challenges; 8) Ensures that activities are successful; 9) Supports a child's intrinsic motivation to play, and 10) Establishes a therapeutic alliance. However, the SIT used in this study was not formally examined by the ASIFM because it had not yet been established. Instead, the first author incorporated the principles of SI (Ayres, 1979; Koomar and Bundy, 1991). For example, the therapist established a safe environment both physically and emotionally, provided praise, feedback, and instruction, made challenges on postural, ocular, and bilateral motor controls, and made appropriative challenges on praxis and organization. The activities were individually planned to present just-right challenges and to tap the client's inner drive, chosen with regard to be client's interest and opinion, consistently modified to succeed and to engage, and designed to offer opportunities for enhanced sensory intake of tactile, vestibular, and proprioceptive information.

The GT programme included social skill training, communication training, kinetic activities, and child–parent play. In this therapy, an occupational therapist, a speech therapist, and three nursery school teachers interacted with five to six challenged children. Because the contents of GT were not adapted to each child, GT only fulfilled parameters "1. Ensures physical safety" and "2. Presents sensory opportunities" in ASIFM.

Instrument

Subjects were assessed using the JMAP (Tsuchida et al., 1989), a re-standardized version of the Miller Assessment for Preschoolers (MAP) for use with Japanese children. The JMAP is composed of the following five major developmental indices: 1) Foundation Index; 2) Coordination Index; 3) Verbal Index; 4) Non-verbal Index; and 5) Complex Index. Items in the Foundation Index evaluate the child's sense of spatial position and movement, sense of touch, and development of the basic components of movement. The Coordination Index includes items that

evaluate gross, fine, and oral motor abilities. The Verbal Index includes items that examine memory, sequencing, comprehension, association, and expression in a verbal context. The Non-verbal Index includes items that test memory, sequencing, visualization, and the performance of mental manipulations not requiring spoken language. The Complex Task Index includes items that measure the combined abilities of sensory motor and cognition (Miller, 1988). Total and Index scores are expressed using percentile scores.

Procedure

The first author, who has been trained to administer and interpret the JMAP, administered the JMAP to all of the subjects individually before and after therapy. Data were excluded for children who could not follow or comprehend the instructions for the JMAP, or whose score was noticeably affected by his inattention, impulsiveness, hyperactivity, or inability to understand the instructions.

Data analysis

The Kolmogorov–Smirnov test indicated that JMAP's Total score and several Index scores for both groups at first examination were not normally distributed. Therefore, we used nonparametric statistics. First, before and after therapy, JMAP data were compared for each group using the Wilcoxon signed-rank test. Next, changes in Total score and each Index score before and after therapy were compared between the SIT group and GT group using Mann–Whitney test.

Results

Subject selection

The Japanese version of the Miller Assessment for Preschoolers data were available from a total of 243 children. Of these children, 84 did not have autistic disorder or Asperger's disorder and were excluded from the present analyses. Of the remaining 159, 29 were excluded for having IQ scores less than 70. From the 130 children left, 78 were excluded for having been tested only once. From the remaining 52, 28 were excluded for having a test–retest period shorter than 8 months or longer than 10 months. Thus, data from the remaining 24 children fulfilled the conditions outlined in the Method section. However, test reports described that several item scores in four cases were lacking in reliability because these subjects had problems in attention or hyperactivity. Therefore, these children were excluded, and the data from the remaining 20 subjects were analyzed in this study. In these subjects, 8 children received individual SIT and 12 children received GT. Seventeen of the subjects who met the inclusion criteria were treated in Nagasaki Prefectural Medical Treatment and Education Center. Twelve children of them received GT and five received SIT. Three children who received SIT were treated in the clinic at Nagasaki University. All individuals who worked with the children (e.g., public health nurses or kindergarten teachers) and all parents had no knowledge of SIT before the first visit. All of the subjects belonged to regular kindergartens or nursery schools, and none of the subjects were medicated. Additionally, no subject had previously received any other type of therapy.

Japanese version of the Miller Assessment for Preschoolers Index score changes before and after therapy within each group

Figure 1 presents mean scores and standard deviations for the SIT group before and after therapy on Total and Index scores on the JMAP. There were significant gains from before to after therapy for Total score (mean gain ± SD = 34.38 ± 21.98) ($W = 36$, $p = 0.012$), Foundation Index score (mean gain ± SD = 34.13 ± 34.21) ($W = 26.5$, $p = 0.035$), Coordination Index score (mean gain ± SD = 46.75 ± 36.26) ($W = 361$, $p = 0.012$), Non-verbal Index score (mean gain ± SD = 45 ± 24.26) ($W = 28$, $p = 0.018$), and Complex Index score (mean gain ± SD = 30.75 ± 20.73) ($W = 28$, $p = 0.018$). However, Verbal Index score showcased no significant changes (mean gain ± SD = 13 ± 44.26) ($W = 24$, $p = 0.401$).

Figure 2 shows mean scores and standard deviations for the GT group before and after therapy on Total and Index scores. While Total score showed a significant gain from before to after therapy (mean gain ± SD = 8.25 ± 11.69) ($W = 43$, $p = 0.015$), Foundation Index score (mean gain ± SD = 11.33 ± 25.54) ($W = 13$, $p = 0.138$), Coordination Index score (mean gain ± SD = 8.92 ± 17.87) ($W = 30.5$, $p = 0.08$), Verbal Index score (mean gain ± SD = 14.67 ± 31.2) ($W = 45$, $p = 0.075$), Non-verbal Index score (mean gain ± SD = 8.25 ± 36.6) ($W = 49$, $p = 0.433$),

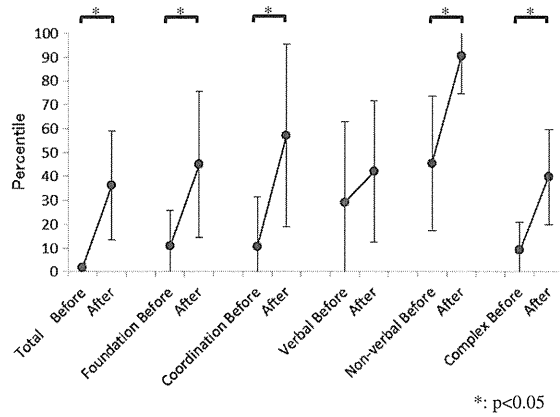

Figure 1 Mean scores and standard deviations for the sensory integration therapy group before and after therapy on Total and Index scores on the Japanese version of the Miller Assessment for Preschoolers

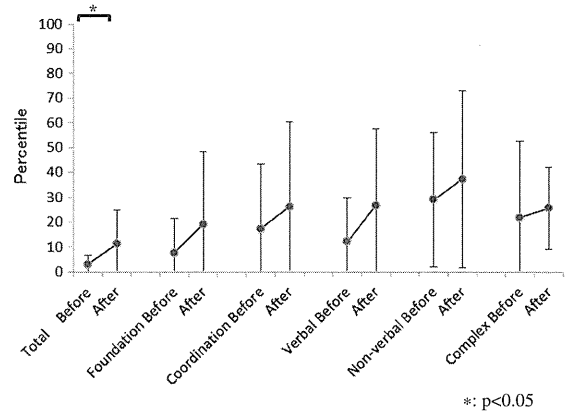

Figure 2 Mean scores and standard deviations for the group therapy group before and after therapy on Total and Index scores on the Japanese version of the Miller Assessment for Preschoolers

and Complex Index score (mean gain ± SD = 3.83 ± 31.2) ($W = 40.5$, $p = 0.505$) showed no significant changes.

Differences in score changes for Total score and each Index score before and after therapy between groups

By using the Mann–Whitney test, significant differences in score changes from before and after therapy between the two groups were found for the Total score ($U = 84$, $p = 0.005$), Coordination Index score ($U = 82$, $p = 0.008$), Non-verbal Index score ($U = 79$, $p = 0.016$), and Complex Index score ($U = 75.5$, $p = 0.034$) with the greater differences occurring in the SIT group compared with the GT group. There were no differences between the two groups for Foundation Index score ($U = 69.5$, $p = 0.086$) or Verbal Index score ($U = 48.5$, $p = 0.969$).

Discussion

The purpose of the present study was to clarify the effectiveness of SIT for children with HFASD. Although the present study did not employ a planned controlled trial, the efficacy of SIT and GT for HFASD was compared by examining differences in JMAP data changes before and after therapy in children with HFASD who had either received SIT or GT by analyzing previously collected data from children with HFASD retrospectively.

In the GT group, Total score was significantly improved from before to after GT; however, there were no significant changes in Index scores. Changes in item scores could not inflate Index scores to a significant level, whereas Total score might change significantly because all item score changes were combined in the Total score. Although the possibility that maturation

or other factors that may produce changes in JMAP scores cannot be ruled out, GT might have little positive affect on abilities that were examined by JMAP. In the SIT group, Total score and all Index scores except for Verbal Index score significantly increased after SIT. The results in score changes from before to after therapy indicated that SIT might improve fundamental sensory-motor abilities, coordination abilities, non-verbal cognitive abilities, and visual-motor abilities.

Comparison of score changes between the SIT group and the GT group using Mann–Whitney analysis showed differences in changes in Total score and three Index scores between the two groups. Because the change in the Coordination Index score was greater in the SIT group than the GT group, the efficacy of SIT for motor coordination abilities in children with HFASD was suggested. The present findings of improved motor coordination with SIT agree with the results of previous studies conducted on children with learning disabilities and mild mental retardation (Humphries et al., 1990; Wilson and Kaplan, 1994; Wuang et al., 2009). The Complex Task Index score was also improved in the SIT group compared with the GT group. Therefore, SIT was suggested to be effective on a combination of motor and cognitive abilities in children with HFASD. The SIT in the present study incorporated principles of SI (Ayres, 1979; Koomar and Bundy, 1991), included activities that were individually planned to present "just-right" challenges, was consistently modified for success and engagement, and made appropriative challenges on praxis and postural, ocular, oral, or bilateral motor control. These elements of SIT might contribute to improved motor abilities and combined abilities in motor and cognition in children with HFASD. Although motor coordination problems are not described in either the diagnostic criteria of Pervasive Developmental Disorder in the DSM-IV (APA, 1994) or ASD in the DSM-5 (APA, 2013), most children with ASD have motor problems. Green et al. (2009) reported that 79% of children with ASD had obvious motor dysfunction. Moreover, Mostofsky et al. (2006) suggested that children with ASD had problems in praxis. Several studies indicated that motor problems affect daily activities. For example, poor motor skills are a strong risk factor for becoming bullied (Bejerot et al., 2011). Children with probable DCD had an increased risk of mental health difficulties in later years (Lingam et al., 2012). Motor impairment in children with DCD was independently associated with lower participation diversity (Fong et al., 2011). Because SIT was demonstrated to be effective in motor coordination and for the combination of motor and cognitive abilities, it might provide a positive impact on abilities related to daily life functions. Changes in Non-verbal Index score from before to after therapy were greater in the SIT group compared with the GT group. Additionally, changes in the Complex Index score that reflect visual-motor function were greater in SIT than GT. Therefore, the effectiveness of SIT for visual cognitive abilities in preschool children with HFASD was suggested.

While three indices significantly changed, the Verbal Index did not showcase any significant differences in the scores from before to after SIT. In addition, there were no differences in the scores between the SIT and GT groups. Therefore, these results suggested that SIT did not improve verbal abilities in children with HFASD. Therefore, the results from the present study might indicate that skills closest to sensory-motor activities related to SIT are more likely to show changes than verbal skills that are further from these training elements.

Although previous work has criticized the efficacy of SIT compared with alternative treatments (Devlin et al., 2011; Section On Complementary And Integrative Medicine; Council on Children with Disabilities; American Academy of Pediatrics et al., 2012), the authors did not examine motor or praxis abilities. To date, there has been no studies examining the efficacy of SIT on motor, praxis, or cognitive abilities of ASD compared with no treatment or alternative treatment using standardized tests. Although the present study could not provide counterevidence for previous critical studies, it demonstrated the efficacy of SIT for motor, visual cognition, and visual-motor abilities, which had not been previously investigated in children with ASD.

The findings of the present study should be interpreted with a few limitations in mind. First, the present study did not compare changes in the score for SIT with other specific therapies. Additionally, the sample size was small, and the present study did not employ a randomized control trial. The number of children in each group was different, because the present study included a retrospective analysis of previously collected data. Both types of therapy were different in their therapy members. Each session length was different (1 h in SIT and 1.5 h in GT). Although treatments were different, there was overlap in that GT training included kinetic activities that were similar

to activities provided in SIT. The same therapist conducted SIT, but multiple staff members took part in GT, because the data were accumulated over a 16-year span. Parents' characteristics such as socioeconomic status were also unavailable. Furthermore, the first author did both testing and SI treatment. This may have biased the findings. Further study should be conducted with a randomized control trial to clarify the differences in the effectiveness of SIT and other forms of therapy for children with ASD.

Conclusion

The present study indicated that SIT was more effective for motor coordination abilities, non-verbal cognitive abilities, and the combined abilities of sensory motor and cognition in children with HFASD when compared with GT. Thus, occupational therapists could use SIT as one technique for the treatment of motor, visual cognition, and visual-motor abilities in preschool children with HFASD.

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