The Change of Asymptomatic Atlantoaxial Instability With Down Syndrome From Infant to Adolescent in Japanese Population: Minimum 10 Years Follow-Up

Masayoshi Machida, MD, Brett Rocos, MD,§ Katsuaki Taira, MD, PhD,* Naho Nemoto, MD,* Noboru Oikawa, MD,* Hirofumi Ohashi, MD, PhD,† Shutaro Aiba, MD,* and Kazuyoshi Nakanishi, MD, PhD‡*

Background: Although 10% to 60% of patients with Down syndrome (DS) develop atlantoaxial instability (AAI), clarifying the course of asymptomatic AAI may prevent unnecessary clinical interactions and investigations. This study investigates the radiographic changes observed in asymptomatic AAI associated with DS in Japanese children as they grow from infancy to adolescence over a minimum of 10 years.

Methods: A retrospective analysis of cervical radiographs acquired from asymptomatic patients with DS in both infancy and adolescence was carried out. Radiographic evaluation included measuring the atlantodental interval (ADI) and the space available for the cord (SAC). In neutral lateral cervical radiographs, AAI was defined as ADI >6 mm and SAC <14 mm.

Results: Two hundred thirty-nine patients were included. The mean follow-up was 12.8 years. ADI was 2.3 mm at initial evaluation and 2.7 mm at final evaluation ($P<0.01$) in a neutral position, 3.1 and 3.3 mm in flexion ($P=0.18$), and 1.7 and 2.1 mm in extension ($P<0.01$), respectively. SAC was 15.8 mm at initial evaluation and 20.9 mm at final evaluation ($P<0.01$) in neutral position, 15.6 and 20.7 mm in flexion ($P<0.01$), and 16.8 and 21.0 mm in extension ($P<0.01$), respectively. Forty-five patients (18.8%) showed evidence of AAI at the initial evaluation with 4 patients meeting the threshold for AAI at the final evaluation, one of which had os odontoideum. In contrast, of the 194 patients who did not have AAI at the initial evaluation, 3 (1.3%) developed AAI at the final evaluation. One of these with a normal den developed AAI at 13 years.

Conclusions: As 1 patient with a normal dens developed AAI at 13 years, we recommend screening for AAI with X-ray in infancy and adolescence regardless of the presence or absence of an os odontoideum.

From the *Department of Orthopaedic Surgery; †Division of Medical Genetics, Saitama Children's Medical Center, Saitama City, Saitama; ‡Department of Orthopaedic Surgery, Nihon University, Tokyo, Japan; and §Division of Spine Surgery, Duke Orthopaedic Surgery, Durham, NC.

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Reprints: Masayoshi Machida, MD, Department of Orthopedic Surgery, Saitama Children's Medical Center, 1-2 Shinntoshin, Chuou-ku, Saitama City, Saitama 330-877, Japan. E-mail: masayoshimachida1985@yahoo.co.jp.

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Although between 10% and 60% of patients with Down syndrome (DS) develop atlantoaxial instability (AAI),[1–6] only 1% to 2% present with symptoms, which can range from minor discomfort to quadriplegia.[7,8] The literature shows that an atlantodental interval (ADI) of between 3.5 and 6 mm is consistent with the condition; however, the precise threshold value for a diagnosis varies by ethnic and physical phenotype.[4,9,10] For the Japanese population, Bouchard et al reported that an ADI >6 mm and space available for the cord (SAC) of <14 mm in a neutral position is an appropriate threshold for diagnosing AAI in DS.[11]

Although the Special Olympics recommend plain radiography to screen for AAI,[12] both the American Academy of Pediatrics and the Faculty of Sports and Exercise Medicine in the United Kingdom (FSEM) no longer do.[13–16] Previous studies reported that AAI tended to improve as patients matured to adolescence, while others contend that this is not so.[2,15,17,18] Although patients with symptomatic AAI need to be followed with regular radiographs, this may be unnecessary in asymptomatic AAI as its course is unknown. This is important as unnecessary screening leads to repeated radiation exposure, excessive medicalization, and disruption of a child's daily living.

Previous analyses have been limited to 5 years of follow-up, which may be insufficient to comprehensively evaluate the natural history of AAI in DS.[15,17,18] The purpose of this study was to compare the radiographic changes observed in asymptomatic AAI from infancy to adolescence in Japanese patients with DS over at least 10 years, to inform the need for regular radiographic monitoring of asymptomatic AAI.

METHODS

Institutional Research Ethics Board approval was obtained. A retrospective analysis of cervical radiographs that were acquired as part of routine care for patients

Table 1 . Patient Demographics

	N = 239
Sex	
Male	130
Female	109
Mean of age at initial evaluation (y)	3.1 ± 0.4 (range: 1.0-4.8)
Mean of age at final evaluation (y)	15.8 ± 1.8 (range: 12.3-19.9)
Mean of follow-up period (y)	12.8 ± 1.7 (range: 10.0-17.0)
Os odontoideum	4

diagnosed with DS in a single center between 2002 and 2024 was carried out. Patients were included if they were diagnosed with DS, had available cervical spine radiographs in neutral, flexed, and extended positions when aged between 1 and 5 years, and another when aged between 12 and 20 years with at least 10 years between them, with no documented symptoms of AAI. Asymptomatic patients were defined as those meeting the criteria for radiographic diagnosis of AAI without complaints and abnormalities of neurological examination such as gait disturbance and hyper-reflexia. Patients were excluded if they had undergone any spinal surgery.

Each radiograph was reviewed by both a board-certified fellowship-trained spine surgeon and a board-certified radiologist. The ADI, and SAC in a neutral, flexed, and extended position of the cervical spine were recorded. The value of ADI and SAC was calculated by taking the mean of the measurements made by the spine surgeon and radiologist. Instability was defined by the criteria set by Bouchard et al in the lateral radiographs (ADI >6 mm, SAC <14 mm in neutral position).[4]

The data were analyzed using R (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria). Distributions of variables are given as means with SD and ranges. Paired t tests, the Fisher exact, and a χ^2 tests were used to assess the significance of any difference in categorical data between infancy and adolescence. P-values of <0.05 were considered to indicate statistical significance. The standard value was defined as average ± 1.96×SD.

RESULTS

Two hundred thirty-nine eligible patients were included (male: 130, female: 109) (Table 1). The mean age at the initial evaluation was 3.1 ± 0.4 years (1.0 to 4.8 y), and at the final follow-up was 15.8 ± 1.8 (12.3 to 19.9 y). The mean follow-up period was 12.8 ± 1.7 years (10.0 to 17.0 y). Four patients were diagnosed with os odontoideum (1.7%).

The mean ADI was 2.3 ± 1.0 mm at initial evaluation and 2.7 ± 1.1 mm at final evaluation ($P<0.01$) in neutral position, 3.1 ± 1.2 mm and 3.3 ± 1.3 mm in flexion ($P=0.18$), and 1.7 ± 0.8 mm and 2.1 ± 0.9 mm in extension ($P<0.01$) (Table 2). SAC was 15.8 ± 2.3 mm at initial evaluation and 20.9 ± 2.7 mm at final evaluation ($P<0.01$) in neutral position, 15.6 ± 2.4 and 20.7 ± 1.3 mm in flexion ($P<0.01$), and 16.8 ± 2.4 and 21.0 ± 2.7 mm in extension ($P<0.01$), respectively. The standard value of ADI was 0.3 to 4.3 mm at initial evaluation and 0.5 to 5.0 mm at final evaluation in neutral position; 0.9 to 5.4 mm and 0.7 to 5.8 mm in flexion; and 0.1 to 3.3 mm and 0.3 to 4.0 mm in extension. The standard value of SAC was 11.2 to 20.3 mm at initial evaluation and 15.6 to 26.2 mm at final evaluation in neutral position; 11.3 to 20.0 mm and 15.6 to 25.8 mm in flexion; and 12.0 to 21.6 mm and 15.7 to 26.4 mm in extension, respectively.

Table 3 shows the change in AAI between initial and final evaluation. Forty-five patients (18.8%) met the criteria for AAI at initial evaluation. One of these had os odontoideum. Four patients continued to meet the criteria for AAI at the final evaluation, one of which showed os odontoideum. The remaining 194 patients did not have AAI at initial evaluation, of which 3 (1.3%) went on to develop AAI by final review. Of these, 2 patients had os odontoideum, and developed AAI at 7 and 12 years, and 1 patient (0.4%) with normal dens developed AAI at 13 years without abnormalities of neurological examination (Fig. 1). In patients without AAI, the standard value of ADI and SAC in neutral position at initial evaluation were 0.7 to 3.4 mm and 13.1 to 20.0 mm, and at final evaluation were 0.8 to 4.4 mm and 16.1 to 26.0 mm.

DISCUSSION

This report describes a consecutive series of patients with AAI in DS from infancy to adolescence. Three patients developed new AAI by final follow-up despite normal radiographs in infancy. This result suggests that asymptomatic patients without evidence of AAI in initial

Table 2. Comparison Between Initial and Final Evaluations in Each Position

	Initial evaluation	Final evaluation	P
Neutral position			
ADI (mm)	2.3 ± 1.0 (range: 0.6-7.8)	2.7 ± 1.1 (range: 1.0-11.7)	<0.01*
SAC (mm)	15.8 ± 2.3 (range: 8.8-23.0)	20.9 ± 2.7 (range: 9.0-28.3)	<0.01*
Flexion position			
ADI (mm)	3.1 ± 1.2 (range: 0.9-9.5)	3.3 ± 1.3 (range: 1.0-12.8)	0.18
SAC (mm)	15.6 ± 2.4 (range: 8.8-22.3)	20.7 ± 1.3 (range: 8.2-27.3)	<0.01*
Extension position			
ADI (mm)	1.7 ± 0.8 (range: 0.4-7.7)	2.1 ± 0.9 (range: 0.6-10.3)	<0.01*
SAC (mm)	16.8 ± 2.4 (range: 8.9-25.4)	21.0 ± 2.7 (range: 10.3-28.8)	<0.01*

ADI indicates atlantodental interval; SAC, space available for the cord.
*Statistic difference at $P<0.05$.

Table 3. The Change of Atlantoaxial Instability

N = 239			
AAI at initial evaluation	45 (Os odontoideum: 1)	AAI at final evaluation	4 (Os odontoideum: 1)
		No AAI at final evaluation	41
No AAI at initial evaluation	194 (Os odontoideum: 3)	AAI at final evaluation	191 (Os odontoideum: 1)
		No AAI at the final evaluation	3 (Os odontoideum: 2)

AAI indicates atlantoaxial instability.

evaluation on childhood images have the risk of developing radiographic AAI on repeat images at a minimum of 10 years later.

The prevalence of AAI at infancy in these data is lower than that described in previous reports,[1–6] because only asymptomatic patients were included. In addition, the prevalence of AAI in adolescence was 2.9%, which was lower than that seen in infancy. However, there remains the possibility that these patients had no complications as a result of their AAI since none of these patients were symptomatic. Nonetheless, this finding agrees with Morton et al who reported that the prevalence of AAI decreases over time.[18] Alongside this, while it has been reported that ADI and SAC can either increase or decrease with growth,[2,17–19] these data suggest that it increases without meeting the threshold for AAI, which in turn causes a decrease in the prevalence of AAI at adolescence. Thus, patients with radiographic evidence of AAI in infancy can be reasonably expected to improve by adolescence in most cases. This should be tempered with the note that while there were statistically significant differences in ADI between infancy and adolescence, the value may lie within the error of measurement even among experts (being as it is <1 mm).

Even when patients do not exhibit any symptoms of AAI, it may be necessary to perform a routine evaluation with an x-ray when an os odontoideum is present. Bauer et al[15] recommended surveillance of asymptomatic patients with an os odontoideum, as these patients show a high rate of developing instability. In addition, the authors reported that although an initial surveillance x-ray for all children over 3 years is recommended by consensus, ongoing screening in patients with a normal dens is not required because of the very low rate of subsequently developing AAI.[15] The FSEM does not recommend plain radiography in those asymptomatic for AAI and suggests that those with DS can participate in sports if the British Gymnastics program and neurological and neck control assessment are satisfied.[16] In contrast, the Special Olympics state that patients with DS may be permitted to participate in the activities if that Athlete undergoes cervical x-ray views in full extension and flexion.[12] In this study, 1 case (0.4%) with normal dens spontaneously developed AAI 13 years after initial screening. Previous reports which followed patients for only 5 years would be insufficient to identify this case.[15–17] On the basis of our results, we recommend that the patients with AAI or os odontoideum in initial screening should be followed closely, and patients with DS without

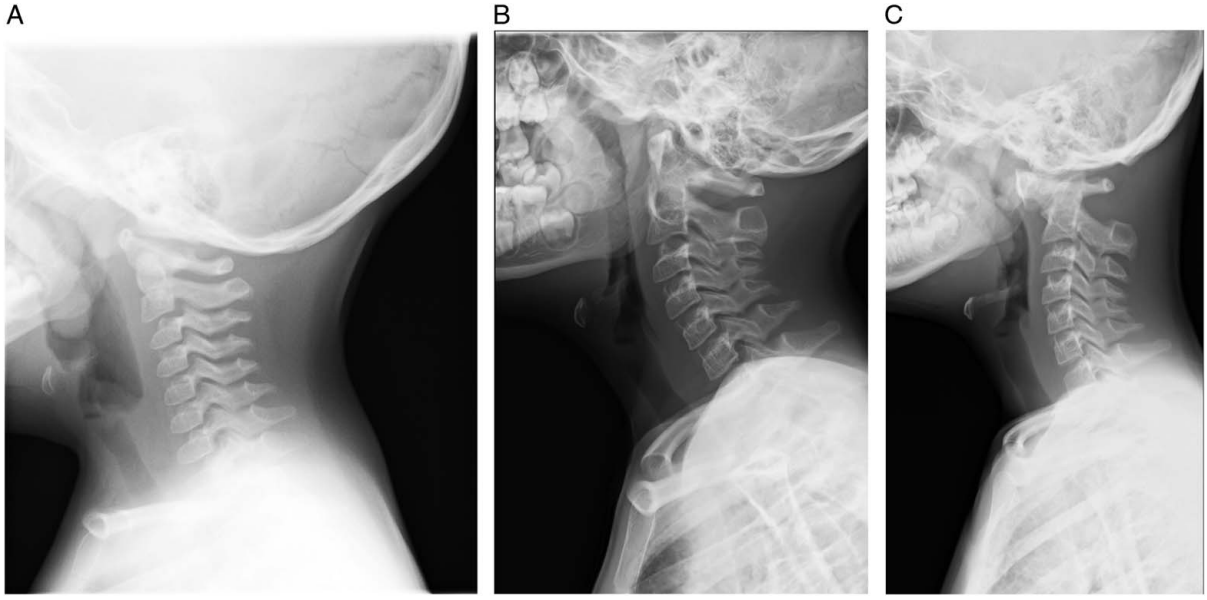

Figure 1. Cervical lateral radiographic in neutral position showing no atlantaxial instability (AAI) at 3 years [atlantodental interval (ADI): 2.5 mm and Space available for the cord (SAC): 16.2 mm] (A), and at 11 years (ADI: 0.9 mm and SAC: 24.5 mm) (B), C, Developed AAI at 13 years with normal dens (ADI: 11.7 mm and SAC: 8.95 mm).

AAI on initial screening be screened twice; once in infancy and once in adolescence, and before participating in sports to comply with athletic regulations. In addition, initial screening should be done at 1 to 5 years, when there is the greatest likelihood of falling due to an unstable gait. The rate of symptomatic AAI with a normal den at final evaluation is only 0.4%, and there are the hurdles of radiation exposure and socioeconomic costs of screening every potential case. Nonetheless, we recommend this algorithm, as the purpose of screening is to diagnose and treat conditions at an early stage.

Furthermore, this report clarifies the standard values of each parameter, which contribute to a better understanding of the concept of hypermobility versus pathologic instability in DS, and helps to establish the range of tolerance to instability that patients with DS can experience without symptoms.

There are limitations in this study in addition to its retrospective design and single-center study. No universally accepted criteria exist for the diagnosis of AAI in flexion and extension radiographs for the Japanese population, as the value for a diagnosis with AAI varies by ethnic and physical phenotype such as physique. Therefore, future work should include a broad range of ethnicities to improve generalizability. In addition, these data could not confirm the differences in radiographic characteristics and demographics between the patients with AAI at the final evaluation without AAI at the initial evaluation and others. Lastly, there may be problems with the inter-rater reliability of the radiographic technique.

In conclusion, these data support the radiographic screening for AAI in patients with DS in both infancy and adolescence regardless of the presence or absence of an os odontoideum.

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