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Allergic status of schoolchildren with food allergy to eggs, milk or wheat in infancy

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Although children allergic to eggs, milk or wheat in infancy tend to become tolerant by school age, the allergic status of these children at school age has not been well evaluated. To investigate the allergic status of schoolchildren who avoided eggs, milk or wheat because of an immediate-type allergic reaction at < 1-yr-old (food avoiders in infancy), we conducted a large-scale questionnaire-based survey of schoolchildren. A questionnaire on allergic diseases was distributed to the parents of 14,669 schoolchildren aged 7 to 15 yr in 30 schools in Kyoto, Japan. Of these, 13,215 responded (response rate, 90.1%). The rate of 7-yr-old children who were food avoiders in infancy was 5.4%. This rate decreased as the current age of the children increased, down to 3% in 15-yr-old children, indicating that food allergy in infancy tended to become more prevalent over the past 8 yr. Although more than 80% became tolerant to these foods by school age, the prevalence of bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis were significantly higher in this group. Moreover, avoidance of other foods (buckwheat, shellfish, fruits and others) at school age was seen at much higher frequencies than in non-food avoiders in infancy (adjusted odds ratio, 7.7; confidence interval, 5.9–10.2). This risk did not differ significantly between those who did and did not develop tolerance to eggs, milk and wheat by 3 yr old. In conclusion, food avoiders in infancy appear to have a higher risk of not only other allergic diseases ('atopic march') but also allergy to other foods ('food allergen march') at school age, indicating the need for continuous attention to food allergy.

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Key words: allergy; atopic march; bronchial asthma; atopic dermatitis; allergic rhinitis; allergic conjunctivitis; epidemiology; food allergy; food avoidance; schoolchildren

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An increasing prevalence and concern about food allergy, especially among children, has been reported in developed countries (1–4). In the United States, food allergy usually starts in infancy as an immediate-type allergy to eggs, milk, peanuts or soy (5). In Japan as well, three major foods (eggs, milk and wheat) have been shown to be the most frequent allergens for immediate-type allergic reactions in infancy (6). Although children allergic to these food allergens in infancy have a tendency to become tolerant by school age (7), patients allergic to other foods, such as peanuts, tree nuts, fish, shellfish and especially buckwheat in Japan (8), are much more likely to maintain their clinical reactivity during or even after school age.

Atopic march usually refers to the tendency of a child with eczema in infancy to develop asthma and allergic rhinitis as he or she becomes older (9, 10). Recent epidemiological studies have shown that the same tendency exists for children with food allergy in infancy. A study of 1749 infants has shown that those with IgE-mediated milk allergy had a significantly increased risk for persistent milk allergy, development of other food allergies, asthma and rhinoconjunctivitis

(11). Also, another study has shown that in 118 children with milk allergy, the children with IgE-positive milk allergy were more likely to have other allergic diseases and sensitization to any allergen by school age (12). Similar increases in respiratory allergic symptoms and aero-allergen sensitization have been shown in infants with egg allergy (13). However, there so far has been a paucity of data regarding risk of other food allergies in school-age children with food allergy in infancy. Thus, it would be clinically important to see whether those who had been allergic to eggs, milk or wheat in infancy had a greater risk for allergy to other food antigens as they grow older, even if they outgrow their initial food allergy.

For that purpose, we investigated the allergic status of schoolchildren who avoided eggs, milk or wheat because of immediate-type allergic reactions at < 1-yr-old (food avoiders in infancy), through analysis of a questionnaire-based survey of more than 13,000 schoolchildren.

Subjects and methods

Epidemiological studies on the prevalence of allergic diseases in schoolchildren

In June 2006, a questionnaire dealing with allergic diseases was distributed through teachers to the parents of all 14,669 children aged 7 to 15 yr attending 30 randomly selected schools in Kyoto, Japan. Informed consent was obtained from the parents who responded to the questionnaires. We collected the questionnaires through the schools. This study was designated as the Allergic Schoolchildren in Kyoto (ASK) study and was approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

Definition of 'food avoiders in infancy' and other allergic diseases

With respect to food allergy, we asked the following questions: (1) Does your child ever have allergic symptoms, such as skin symptoms like hives or respiratory symptoms like cough/wheeze, within 1 to 2 h after ingesting a particular food? (2) Does your child avoid particular foods due to these symptoms? (3) If so, what are the kinds of foods and the duration of avoidance? Those who answered 'yes' to both questions 1 and 2 were regarded as having either a past history or present illness of immediate-type food allergy, and the kinds of foods avoided were tabulated. Among them, those who avoided any of the three major food allergens (eggs, milk or wheat) from < 1 yr of age were defined as 'food avoiders in infancy'. These three foods were chosen because, among 589 subjects who avoided any foods from < 1 yr of age, 551 subjects (93.5%) avoided either eggs (n = 439), milk (n = 202) or wheat (n = 114), indicating that these are exclusively important food allergens during infancy in Japan, as shown previously (6). The food avoiders in infancy were further divided into two subgroups, depending on whether they developed early tolerance (avoidance could be terminated for all three foods by 3 yr old). The questionnaire on the prevalence of four other allergic diseases [bronchial asthma (BA), atopic dermatitis (AD), allergic rhinitis (AR) and allergic conjunctivitis (AC)] was based on and comparable to the one used by the International Collaborative Study of Asthma and Allergies in Childhood (ISAAC) (14) and was prepared and validated by the Study Group of Epidemiology of Allergic Diseases founded by the Japanese Ministry of Public Health and Welfare in 1993 (15). Definitions of these allergic diseases based on the questionnaire are described elsewhere (16).

Statistical analysis

Following the descriptive statistics, we developed univariate and multivariate logistic regression models to evaluate the effects of early food avoidance on present food avoidance and other allergic diseases. The dependent variables included bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis, and the independent variables included age, gender and birth order. p-values < 0.05 were considered statistically significant. All statistical analyses were carried out using SAS software (Version 9.1; SAS Institute Inc., Cary, NC, USA).

Results

A total of 13,215 questionnaires were collected (response rate, 90.1%). The rate of food avoiders in infancy was 5.4% in 7-yr-old children. This rate decreased as the current age of the children increased, down to 3% in 15-yr-old children (Fig. 1). The overall rate of food avoiders in infancy was 4.2%. Sex ratio (male/female) and age distribution (y, mean ± standard deviation) of food avoiders in infancy vs. non-food avoiders in infancy were 1.35 vs. 1.02 ($p = 0.02$) and 9.3 ± 2.4 vs. 9.9 ± 2.5 ($p < 0.0001$), respectively, indicating that there were significantly

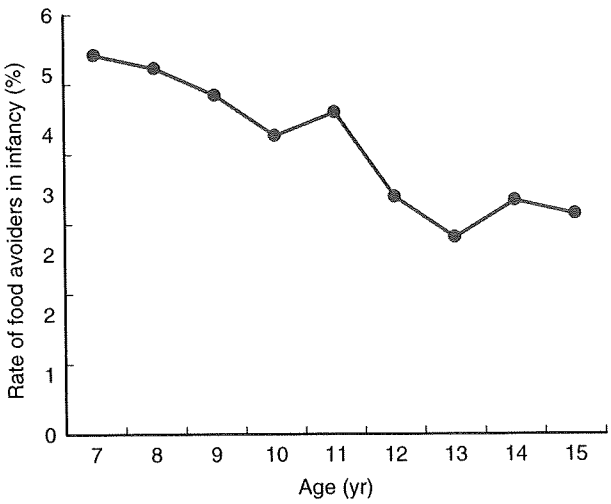

Fig. 1. Rate of food avoiders in infancy according to present age.

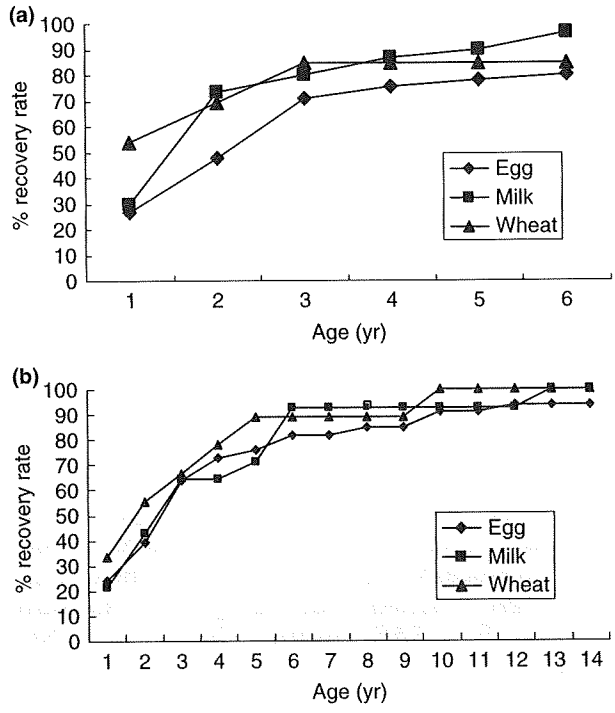

Fig. 2. Recovery from egg, milk or wheat avoidance according to age. Data with food avoiders in infancy now at (a) 7 yr olds and (b) 15 yr olds are shown.

more male and younger children among food avoiders in infancy. Analysis of the age at which the avoidance was terminated showed that more than 80% became tolerant to these foods by school age (Fig. 2). However, prevalence of BA, AD, AR and AC were significantly higher in food avoiders in infancy (Table 1) at school age, both by univariate and multivariate analysis. In these analyses, the adjusted odds ratio was highest in AD (3.18), followed by BA (2.68), AC (1.76) and AR (1.57).

Moreover, present avoidance of other foods was seen at much higher frequencies in food avoiders in infancy compared to non-food avoiders in infancy (adjusted odds ratio, 7.7; confidence interval, 5.9–10.2) at school age (Table 2). Foods other than eggs, milk and wheat were avoided in 17.0% of food avoiders in infancy, whereas only 1.9% of non-food avoiders in infancy refrained from eating these foods. These risks did not differ significantly in those with or without early tolerance (Table 3).

The frequencies of the kinds of other foods that were avoided are shown in Fig. 3. The most frequently avoided food was buckwheat, followed by shellfish and fruit in both groups. Compared to children in the United States, relatively fewer children avoided peanuts.

There was a striking difference in the age distribution at which the present avoidance of other foods was started. While 54% started avoiding those foods at the age of 4 yr or more in non-food avoiders in infancy, 52% started at <1 yr old in food avoiders in infancy (Fig. 4).

Discussion

The rate of food avoiders in infancy decreased as the current age of the children increased, confirming a rising trend of food allergy in infancy over the past 8 yr. More than 80% of this population outgrew allergies to eggs, milk and wheat by school age, which is in accordance with most of the previous studies, but contrary to the

Table 1. Prevalence of allergic diseases in schoolchildren with or without food avoidance in infancy

	Food avoiders in infancy (n = 556)	Non-food avoiders in infancy (n = 12,659)	p-value (univariate)	p-value (multivariate)*	Adjusted OR	95% CI
BA	95 (17.1%)	569 (4.5%)	<0.0001	<0.0001	2.68	2.08–3.46
AD	106 (19.1%)	629 (5.0%)	<0.0001	<0.0001	3.18	2.50–4.04
AR	263 (47.3%)	3358 (26.5%)	<0.0001	<0.0001	1.57	1.29–1.91
AC	245 (44.1%)	3079 (24.3%)	<0.0001	<0.0001	1.76	1.45–2.15

OR, odds ratio; CI, confidence interval; BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis.
*Adjusted for age, gender, birth order and other allergic diseases.

Table 2. Present food avoidance (other than eggs, milk or wheat) in schoolchildren with or without food avoidance in infancy

	Food avoiders in infancy (n = 556)	Non-food avoiders in infancy (n = 12,659)	p-value (univariate)	p-value (multivariate)*	Adjusted OR	95% CI
Present food avoidance (other than eggs, milk or wheat)	94 (17.0%)	243 (1.9%)	<0.0001	<0.0001	7.72	5.87–10.16

OR, odds ratio; CI, confidence interval.
*Adjusted for age, gender, birth order and other allergic diseases.

Table 3. Present food avoidance (other than eggs, milk or wheat) in food avoiders in infancy with or without early tolerance

	Early tolerance*		p-value		
	Yes (n = 362)	No (n = 194)	(univariate)	OR	95% CI
Present food avoidance (other than eggs, milk or wheat)	64 (17.7%)	30 (15.5%)	0.51	0.85	0.53–1.37

OR, odds ratio; CI, confidence interval.
*Early tolerance means that avoidance could be terminated for all three foods by 3 yr old.

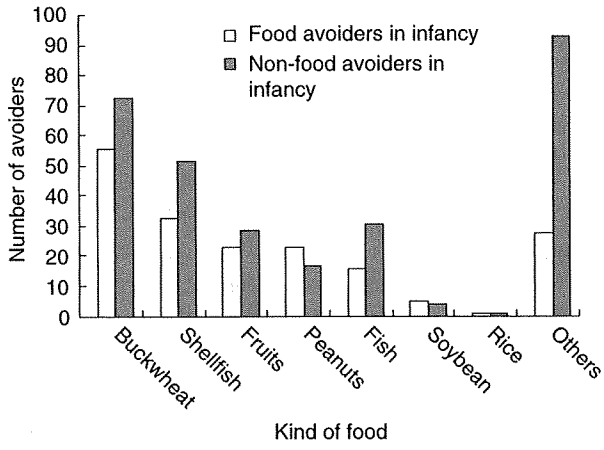

Fig. 3. Distribution of foods, other than eggs, milk or wheat, being avoided at present.

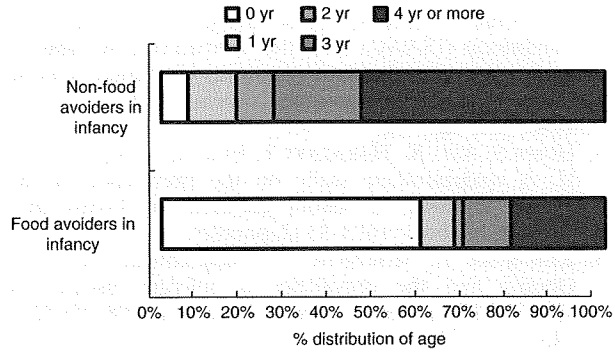

Fig. 4. Distribution of starting age for food avoidance other than eggs, milk or wheat.

recent reports by Skripak et al. (17) who showed that rates of resolution of milk allergy were only 42% and 64% by age 8 and 12 yr respectively. As their study design is a retrospective review of the clinical records of two tertiary care centres, possible population bias toward more severe cases might explain the different results. As expected from the recent literature (11–13), food avoiders in infancy appear to have a higher risk of other allergic diseases at school age. AD was most strongly linked to food avoidance in infancy, supporting the proposed relationship between food allergy and AD (18). Our data also showed that food avoiders in infancy avoid other foods at much higher frequency at school age, suggesting the existence of not only 'atopic march' but also 'food allergen march'. Moreover, the risk of present food avoidance did not differ significantly between those with and without early food tolerance, indicating that food avoiders in infancy are at risk of having food allergy from other causes at school age, whether they could achieve tolerance to eggs, milk and wheat at earlier ages (< 3 yr old) or not.

Differences in ages at which the present food avoidance started suggest that food avoiders in infancy develop symptoms of other food allergies at a much lower age. There might be some genetic predisposition to allergies to various kinds of foods in these individuals. In this respect, we previously reported that *SPINK5* polymorphism, known to cause skin barrier dysfunction, was associated not only with AD but also with food allergy (19), suggesting the existence of genetic barrier dysfunction of not only skin but also intestinal epithelium.

An alternative explanation to the association between early and present food avoidance might be that parents of food avoiders in infancy tend to avoid other foods with only subtle, 'possibly

allergic' symptoms at a much lower age because of concerns about food allergy. Actually, a population-based study of 798 6-yr-old children in the United Kingdom revealed that the rates of perception of food hypersensitivity are higher than the prevalence of sensitization to main food allergens and the prevalence of food hypersensitivity based on food challenges (4). The possible overconcern might be associated with the notion that the foods avoided at present, such as buckwheat, shellfish and fish, cause more severe anaphylactic reactions (20). Thus, appropriate medical assessment, such as measurement of allergen-specific IgE and food challenge tests, should be performed and unnecessary food avoidance, if any, be discontinued, because food avoidance has been shown to negatively affect health-related quality of life in children (21). Also, food avoidance may cause growth disturbance (22) and psychological burden (23) in children.

One limitation of the study is that the validity of food avoidance in infancy cannot be confirmed by physician diagnosis or any laboratory data because it is a large population-based questionnaire survey. However, parents were asked about the existence of food-induced allergic reactions, and those avoiding foods without any food-specific immediate-type reactions were excluded from the analysis, making the data more reliable than simply including all those who avoided foods in the analysis. In support of this, the rate of food allergy prevalence of 3% to 5% in infancy in our data is comparable with other recently reported prevalence rates (1, 24). Another limitation is possible recall bias, in which parents of food avoiders in infancy might remember more about their children's allergic diseases, although we do not think it is a significant concern because we defined the presence of each disease based on the existence of current symptoms deliberately described in the questionnaire (16), which is unlikely to be affected by the parent's memory.

In conclusion, our data clearly show the significant link between food allergy to eggs, milk or wheat in infancy and that to other foods at school age and calls for continuous attention to food avoiders in infancy up to school age, with respect not only to other allergic diseases but also to other food allergies.

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References

1. Venter C, Pereira B, Voigt K, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. Allergy 2007: 63: 354–9.
2. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. J Allergy Clin Immunol 2007: 120: 491–503.
3. Keil T. Epidemiology of food allergy: what's new? A critical appraisal of recent population-based studies. Curr Opin Allergy Clin Immunol 2007: 7: 259–63.
4. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. Pediatr Allergy Immunol 2006: 17: 356–63.
5. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. J Allergy Clin Immunol 1999: 104: S114–22.
6. Imai T, Iikura Y. The national survey of immediate type of food allergy. Arerugi 2003: 52: 1006–13 (Japanese).
7. Ramesh S. Food allergy overview in children. Clin Rev Allergy Immunol 2008: 34: 217–30.
8. Shek LP, Lee BW. Food allergy in Asia. Curr Opin Allergy Clin Immunol 2006: 6: 197–201.
9. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006: 118: 209–13.
10. Spergel JM. Atopic march: link to upper airways. Curr Opin Allergy Clin Immunol 2005: 5: 17–21.
11. Høst A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunol 2002: 13 (Suppl. 15): 23–8.
12. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol 2005: 116: 869–75.
13. Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. Pediatr Allergy Immunol 2000: 11: 162–7.
14. The international study of asthma and allergies in childhood (ISAAC) steering committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998: 351: 1225–32.
15. Hosoi S, Asai K, Harazaki T, Furushou K, Mikawa H. A epidemiologic study on the prevalence of the allergic diseases in school children in Kyoto city. Arerugi 1997: 46: 1025–35 (Japanese).
16. Kusunoki T, Morimoto T, Nishikomori R, et al. Obesity and the prevalence of allergic diseases in schoolchildren. Pediatr Allergy Immunol 2008: 19: 527–34.
17. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. J Allergy Clin Immunol 2007: 120: 1172–7.
18. Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. Pediatr Allergy Immunol 2004: 15: 421–7.
19. Kusunoki T, Okafuji I, Yoshioka T, et al. SPINK5 polymorphism is associated with disease severity and

food allergy in children with atopic dermatitis. J Allergy Clin Immunol 2005: 115: 636–8.
20. Wang J, Sampson HA. Food anaphylaxis. Clin Exp Allergy 2007: 37: 651–60.
21. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy 2008: 63: 211–8.
22. Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. J Am Diet Assoc 2002: 102: 1648–51.
23. Teufel M, Biedermann T, Rapps N, et al. Psychological burden of food allergy. World J Gastroenterol 2007: 13: 3456–65.
24. Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004: 113: 805–19.

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Successful autologous peripheral blood stem cell transplantation with a double-conditioning regimen for recurrent hepatoblastoma after liver transplantation

Niwa A, Umeda K, Awaya T, Yui Y, Matsubara H, Hiramatsu H, Watanabe K-I, Adachi S, Itoh T, Uemoto S, Nakahata T. Successful autologous peripheral blood stem cell transplantation with a double-conditioning regimen for recurrent hepatoblastoma after liver transplantation.
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Abstract: A four-yr-old boy developed a solitary metastasis nine months after living-related liver transplantation for unresectable hepatoblastoma. After resection of the metastatic lesion, he received an auto-PBSCT with a double-conditioning regimen consisting of melphalan and thiotepa. Auto-PBSCT could be safely performed without any serious regimen-related toxicity or infection. However, transient cessation of tacrolimus during myelosuppression resulted in graft rejection of the liver just after hematological engraftment, but rejection was resolved by tacrolimus and methylprednisolone. The patient is alive and free from disease two yr after auto-PBSCT without any signs of graft rejection. High-dose chemotherapy using this conditioning regimen may be feasible for recurrent hepatoblastoma after liver transplantation in terms of safety and anti-tumor activity.

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Key words: hepatoblastoma – high-dose chemotherapy – double-conditioning regimen – liver transplantation

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Hepatoblastoma is a common malignant tumor in childhood. Combination of multidrug chemotherapy and surgical resection has improved the survival rates up to 70% (1, 2). Furthermore, LT has recently contributed to the elevation of cure rates for patients with an unresectable tumor. The prognosis of relapse cases after LT, however, remains dismal and the treatment of such cases has not been established (3, 4). Here, we report a case that underwent auto-PBSCT with high-dose chemotherapy for recurrent hepatoblastoma after LT and discuss the role of high-dose chemotherapy for such cases.

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; auto-PBSCT, autologous peripheral blood stem cell transplant; CBDCA, carboplatin; CDDP, cisplatin; CMV, cytomegalovirus; CT, computer tomography; EBV, Epstein–Barr virus; G-CSF, granulocyte-stimulating factor; GGT, gamma glutamyl transferase; HLA, human leukocyte antigen; IFO, ifosfamide; JPLT, Japanese Study Group for Pediatric Liver Tumor; LDH, lactate dehydrogenase; L-PAM, melpharan; LRLT, living-related liver transplantation; LT, liver transplantation; mPSL, methylprednisolone; PBSC, peripheral blood stem cell; TEPA, thiotepa; THP-ADR, tetrahydropyranyl-adriamycin; VOD, veno-occlusive disease.

Case report

A four-yr-old boy with an abdominal mass was diagnosed with embryonic hepatoblastoma by liver biopsy. At the time of diagnosis, the AFP level was 1 880 000 ng/mL. Abdominal CT showed that the tumor involved both lobes, which was categorized as pretreatment extent of disease system (PRETEXT) III (5). There was no metastatic disease detected by bone scintigraphy or chest CT scan. He was treated with two courses of CDDP 80 mg/m^2 on day one and THP-ADR 30 mg/m^2 on days one and two, and three courses of IFO 3 g/m^2 on days one and two, CBDCA 400 mg/m^2 on day three,

THP-ADR 30 mg/m^2 on days four and five, and etoposide (VP16) 100 mg/m^2 on days 1–5, according to the JPLT protocol (6), and with additional two courses of irinotecan (CPT-11) 20 mg/m^2 daily for five days. Even after those therapies, however, the size of the tumor did not change, and the AFP level remained high at 170 000 ng/mL.

At the age of four yr and eight months, the patient was transferred to our hospital for treatment of unresectable hepatoblastoma. He underwent LRLT from his mother and was treated with three courses of CPT-11 at 20 mg/m^2 daily for five days post-operatively. The AFP level normalized, and abdominal and chest CT scans showed no evidence of disease. He received tacrolimus orally and there was no sign of graft rejection.

Nine months after LRLT, the AFP levels increased to 68 ng/mL, and chest CT demonstrated a solitary tumor measuring 6.5 mm in the upper lobe of left lung. He underwent a wedge resection of left lung and histological examination of the tumor confirmed relapse of the disease. As the tumor is thought to be at least partially resistant to the standard chemotherapy used prior to LT, we planned to use L-PAM and TEPA with stem cell rescue, both of which had not been used and were expected to retain anticancer effect. Thereafter, PBSC containing 5.1 × 10^6 cells/kg CD34$^+$ cells were harvested after mobilization with nogitecan at 1 mg/m^2 daily for five days and G-CSF.

The clinical course of auto-PBSCT is shown in Fig. 1. For fear of a higher risk of severe regimen-related toxicity, the patient received a modified double-conditioning regimen (two cycles of drug combinations with a one-wk interval) that was originally reported by Hara et al. (7).

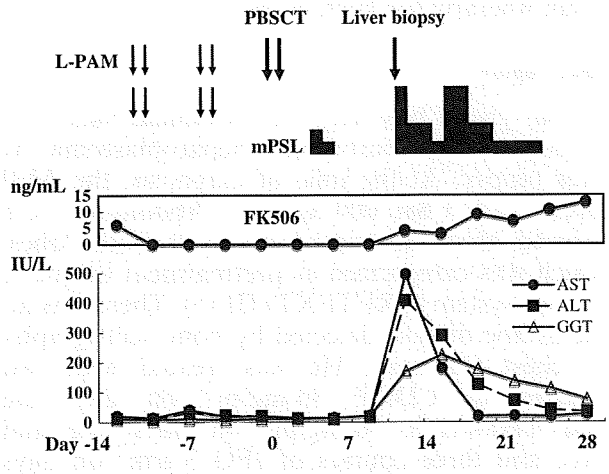

Fig. 1. The clinical course of auto-PBSCT after LT.

The regimen consisted of 50 mg/m^2 L-PAM on days 11, 10, four, and three; TEPA of 150 mg/m^2 on days 11 and 10 and 200 mg/m^2 on days four and three. He also received ursodeoxycolic acid, low-molecular-weight heparin, antithrombin III for prophylaxis for VOD of the liver. Tacrolimus was discontinued just before the start of conditioning for fear of severe renal toxicity because of concomitant administration of L-PAM. PBSC containing 3.3 × 10^6/kg CD34$^+$ cells were infused, and G-CSF was started from day six until engraftment.

Hematological engraftment was prompt; absolute neutrophil counts reached more than 0.5 × 10^9/L on day 10; reticulocytes were more than 10‰ on day 14; platelet counts were more than 5.0 × 10^9/L on day 10. There were no severe regimen-related toxicities, such as mucositis, renal toxicity, or VOD, and no severe infections.

Pyrexia occurred on day four, and was diagnosed as clinical engraftment syndrome. The patient was treated with mPSL intravenously for four days starting on day five, which improved the symptom. Although tacrolimus was resumed on day 11, marked elevation of serum AST (477 IU/L), ALT (452 IU/L), LDH (654 IU/L), ALP (831 IU/L), and GGT (187 IU/L) levels occurred on the same day. Abdominal CT scan showed normal findings and there was no reactivation of CMV or EBV. He was diagnosed as having mild acute cellular rejection based on histological examination of a liver biopsy specimen (Fig. 2). mPSL was given intravenously for 10 days starting on day 11, and liver dysfunction rapidly improved. The patient was alive and free from disease two yr after the auto-PBSCT with no signs of graft rejection.

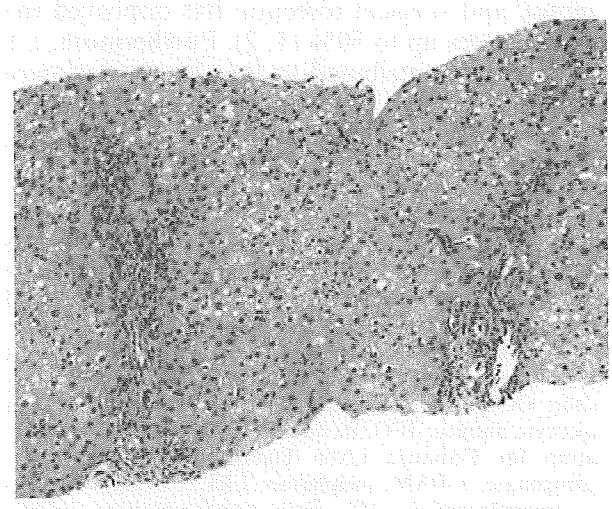

Fig. 2. Histology of liver biopsy on day 11 showing a predominantly lymphocyte infiltration in portal tracts, which was diagnosed as acute cellular graft rejection.

Discussion

Chemotherapy has improved the prognosis of hepatoblastoma (1, 2). However, the outcome of chemoresistant cases remains extremely poor, and effective treatment for such cases has not been established. Although the role of high-dose chemotherapy in the treatment of hepatoblastoma remains controversial, there are some reports describing auto-PBSCT for hepatoblastoma (7–9). Our case underwent LRLT but a solitary lung metastasis developed. Although the metastatic lesion could be removed completely, the prognosis was thought to be poor, since previous reports indicated that most patients with relapse after LT died their disease (4). Moreover, these cases were thought to be resistant to CDDP, THP-ADR, IFO, CBDCA, and VP16 at standard doses, which are the key drugs to treat hepatoblastoma. Therefore, we used high-dose chemotherapy with stem cell rescue using two alkylating agents, L-PAM and TEPA, which had not been used in this case and are reported to have potent anti-tumor activity (7).

There has not been any report of successful auto-PBSCT after LT. Compared with conventional auto-PBSCT, it remains unknown whether the preconditioning regimen could be tolerated by patients with a transplanted liver. Double-conditioning regimen (two cycles of drug administration with a one-wk interval), a modification of the treatment reported by Hara et al. (7), was selected to reduce regimen-related toxicities to a minimum while retaining the anti-cancer effect. Indeed, there was no serious regimen-related toxicity in this case. There was no severe infection either, despite using immunosuppressive agents to prevent graft rejection after LT. Although the follow-up period remains relatively short, high-dose chemotherapy with auto-PBSCT might be effective as a consolidation therapy after resection of a metastatic lesion. Thus, high-dose chemotherapy with stem cell rescue could be considered for cases with metastatic or relapsed tumors that were resistant to the standard chemotherapy.

Even in conventional auto-PBSCT, the combination of L-PAM and TEPA has been reported to cause severe renal toxicity (7). To reduce the risk of severe renal toxicity, the total dose of L-PAM was reduced from 280 mg/m^2, that was originally reported (7), to 200 mg/m^2. Furthermore, to gain sufficient time for the elimination of L-PAM, tacrolimus was discontinued from the beginning of the conditioning regimen until hematological engraftment. As a result, graft rejection did occur on day 11 although it had not previously been observed before auto-PBSCT. In cases undergoing allogeneic BMT from HLA-matched sibling donor after LT, graft rejection was not reported when immunosuppressive agents were transiently discontinued during administration of preconditioning drugs, then restarted from one day before transplantation (10, 11). Therefore, it is suggested that at the early stage of auto-PBSCT, only a few engrafted cells can cause graft rejection in the absence of immunosuppressive agents. Low dose of tacrolimus or steroids after conditioning might reduce the risk of graft rejection.

In conclusion, we successfully performed auto-PBSCT after the double-conditioning regimen with L-PAM and TEPA for recurrent hepatoblastoma after LT. If the patient is in good condition, the conditioning regimen with L-PAM and TEPA can be performed safely after LT, and possibly prevent relapse of hepatoblastoma that is refractory against standard chemotherapies. More sophisticated immunosuppressive therapy after conditioning will be required to prevent graft rejection.

References

1. von Schweinitz D, Byrd DJ, Hecker H, et al. Efficiency and toxicity of ifosfamide, cisplatin, and doxorubicin in the treatment of childhood hepatoblastoma. Eur J Cancer 1997: 33: 1243–1249.
2. Carceller A, Blanchradh H, Champagne J, et al. Surgical resection and chemotherapy improve survival rate for patients with hepatoblastoma. J Pediatr Sur 2001: 36: 755–759.
3. Otte JB, Pritchard J, Aronson DC, et al. Liver transplantation for hepatoblastoma: Results from the International Society of Pediatric Oncology (SIOP) Study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 2004: 42: 74–83.
4. Kasahara M, Ueda M, Haga H, et al. Living-donor liver transplantation for hepatoblastoma. Am J Transplant 2005: 5: 2229–2235.
5. Aronson DC, Schnater JM, Staalman CR, et al. Predictive value of the pretreatment extent of disease system in hepatoblastoma: Results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 Study. J Clin Oncol 2005: 23: 1245–1252.
6. Sasaki F, Matsunaga T, Iwafuchi M, et al. Outcome of hepatoblastoma treated the JPLT-1 (Japanese Study Group for Pediatric Liver Tumor) Protocol-1: A report from the Japanese Study Group for Pediatric Tumor. J Pediatr Surg 2002: 37: 851–856.
7. Hara J, Osugi Y, Ohta H, et al. Double-conditioning regimens consisting of thiotepa, melphalan and busulfan with stem cell rescue for the treatment of pediatric solid tumors. Bone Marrow Transplant 1998: 22: 7–12.
8. Yoshinari M, Imaizumi M, Hayashi Y, et al. Peripheral blood stem cell transplantation for hepatoblastoma with microscopic residue: A therapeutic approach for incompletely resected tumor. Tohoku Exp Med 1998: 184: 247–254.

9. Nishimura SI, Sato T, Fujita N, et al. High-dose chemotherapy in children with metastatic hepatoblastoma. Pediatr Int 2002: 44: 300–305.
10. Chiang KY, Lazarus HM. Should we be performing more combined hematopoietic stem cell plus solid organ transplants? Bone Marrow Transplant 2003: 31: 633–642.
11. Umeda K, Adachi S, Watanabe K, et al. Successful hematopoietic stem cell transplantation for aplastic anemia following living related liver transplantation. Bone Marrow Transplant 2002: 30: 531–534.

TABLE 2 Details of response to sequential treatments where applicable ($n = 10$)

No.	Severity of disease	First treatment		Second treatment		Third treatment	
1	Severe	Amlodopine	×	Nifedipine	√	–	–
2	Moderate	Amlodopine	×	GTN	×	–	–
3	Moderate	Amlodopine	×	GTN	×	–	–
4	Severe	Nifedipine	×	Amlodopine	×	–	–
5	Severe	Nifedipine	×	Amlodopine	×	GTN	√
6	Moderate	Nifedipine	×	GTN	×	–	
7	Severe	GTN	×	Amlodopine	×	Nifedipine	√
8	Moderate	Nifedipine	×	GTN	√	–	–
9	Severe	Amlodopine	×	Nifedipine	×	GTN	×
10	Moderate	Amlodopine	√	GTN	√	–	–

×: no response/inadequate response; √: response.

Overall, GTN patches were effective in 55% of the treated patients. Efficacy was better than that of nifedipine and amlodipine (33 *vs* 25% response rate, respectively), but small numbers and retrospective analysis does not allow statistical comparison. Response was similar in primary and secondary RP. Children with severe RP had a better response to nifedipine and amlodopine than children with moderate disease. The sub-group with severe disease was more likely to be using a disease-modifying drug, which may have had an impact. However, numbers are too small for any conclusion to be drawn from this.

Application of GTN patches allows removal if adverse events occur. Together with absence of tablets, this may make treatment with GTN attractive in paediatric practice. All patients received Deponit GTN patches. Alternative brands may not have adequate skin adhesion when cut into quarters for this off-license use.

GTN patches, nifedipine and amlodipine offer symptomatic relief for patients with moderate primary/secondary RP. Further studies, including head-to-head trials, are needed to determine if one agent is superior. Meanwhile, GTN patches offer an alternative to oral calcium channel blockers for symptomatic relief of paediatric RP.

Rheumatology key message

- GTN patches are an efficacious treatment option in paediatric RP.

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References

1 Anderson ME, Moore TL, Hollis S, Jayson MIV, King TA, Herrick AL. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. Rheumatology 2002;41:324–28.

2 Franks AG Jr. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. Lancet 1982;1:76–7.

3 Teh LS, Mannig J, Moore T, Tully MP, O'Reilly D, Jayson MIV. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. Br J Rheumatol 1995; 34:636–41.

4 Nigrovic PA, Fuhlbrigge RC, Sundel RP. Raynaud's phenomenon in children: a retrospective review of 123 patients. Pediatrics 2003;111:715–21.

5 Coppock JS, Hardman JM, Bacon PA, Woods KL, Kendall MJ. Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. Postgrad Med J 1986;62:8–15.

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A case of early-onset sarcoidosis with a six-base deletion in the *NOD2* gene

SIR, We present the first case of early-onset sarcoidosis (EOS, MIM no. 609464) with a six-base deletion in the *NOD2* gene, resulting in the replacement of one amino acid and the deletion of two additional amino acids. All previous mutations reported for EOS and Blau syndrome (BS, MIM no. 186580) were single-base substitutions that resulted in the replacement of a single amino acid [1–3].

The patient was a Japanese male born after an uncomplicated pregnancy and delivery. His family had no symptoms of skin lesions, arthritis or uveitis. At 5 years of age, he was diagnosed with bilateral severe uveitis. He became blind in both eyes during adolescence. He had swollen ankles without pain during childhood,

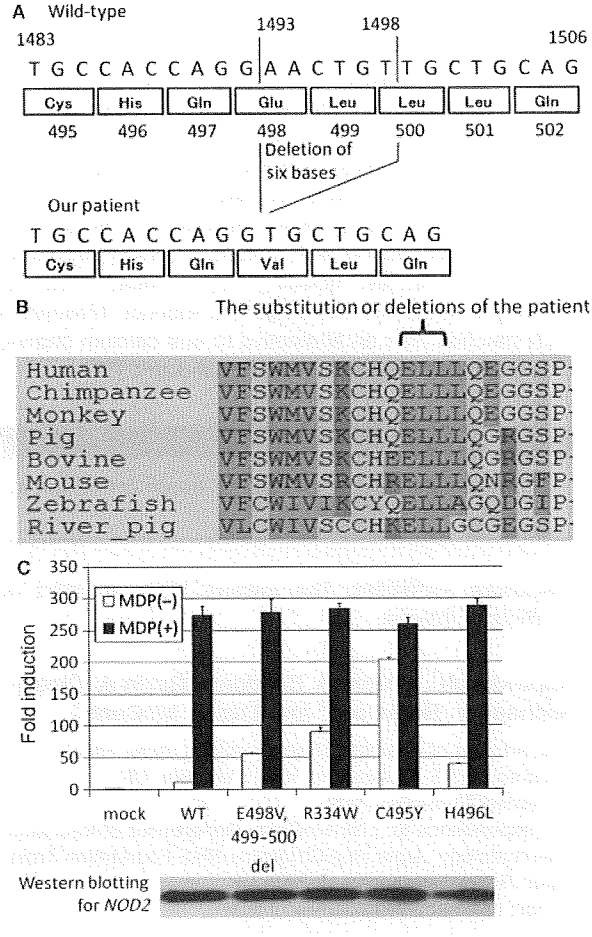
and developed arthritis in his both knees and ankles at 15 years of age. At 30 years, a skin rash had developed on his extremities after his first BCG vaccination. The skin lesions were scaly erythematous plaques with multiple lichenoid papules and some pigmentation. At the same age, camptodactyly without obvious synovial cysts of the hands was observed, and the deformity in all fingers developed by 35 years. At 41 years, he had low-grade fever for 1 year. He had no pulmonary lesions. His laboratory investigations showed normal white blood cell count, mildly elevated CRP (1.0 mg/dl) and ESR (20 mm/h). A skin biopsy from his left forearm revealed non-caseating granulomas without lymphocyte infiltration. There were no indications of infection by *Mycobacterium*.

The clinical symptoms and pathological findings on the biopsied skin indicated that the patient suffered from EOS. It has been reported that EOS and BS have a common genetic aetiology due to mutations in the *NOD2* gene that cause constitutive Nuclear Factor (NF)-κB activation [4, 5]. Thus we analysed the *NOD2* gene from the patient to look for mutations that might correlate with the pathology of EOS. A written informed consent was obtained from the patient and his families, according to the protocol of the institutional review board of Kyoto University Hospital and in accordance with the Declaration of Helsinki. Genomic sequencing analysis of the patient's *NOD2* gene showed the presence of a heterozygous deletion of six bases in exon 4, which resulted in c.1493_1498delAACTGT, p.E498V, 499–500del (Fig. 1A). The mutation was novel and was not identified in 100 normal controls. A genome alignment of *NOD2* among several species showed that E498, L499 and L500 are conserved from zebrafish to human (Fig. 1B). These data strongly suggested that the identified deletion of six bases in the *NOD2* gene is not a single nucleotide polymorphism (SNP), but is probably responsible for EOS in the patient.

Previous studies report that *NOD2* mutations causing EOS/BS show constitutive activation of NF-κB [6–8]. Therefore, we investigated the level of NF-κB activity associated with the new mutation identified here. First, we confirmed the level of mRNA expression of the mutated allele by subcloning analysis of *NOD2*-cDNA, which showed that the mutated allele was expressed as well as the wild type allele (data not shown). We then evaluated the ability of the *NOD2* mutant to constitutively activate NF-κB by using an *in vitro* reporter system in HEK293T cells transfected with both *NOD2* mutants and NF-κB reporter plasmids (Fig. 1C). The deletion mutant demonstrated almost five times more NF-κB activity than wild type without muramyl dipeptide (MDP) stimulation. Western blot analysis confirmed that NOD2 mutant protein expression was similar to that of wild type (Fig. 1C). Thus, like other mutations of *NOD2* identified previously, the deletion mutant identified here also showed constitutive activation of NF-κB.

The mechanism underlying EOS/BS has not been totally understood, although two pathways downstream from *NOD2* have been identified: NF-κB activation through receptor-interacting protein (RIP) like interacting caspase-like apoptosis regulatory protein kinase (RICK) and MAP kinase activation through the caspase recruitment domain 9 (CARD9) [9]. We previously tested 10 *NOD2* missense mutations that have been identified in our cohort of EOS/BS patients in Japan, and all of them demonstrated constitutive activation of NF-κB [3]. By analysing this newly identified deletion mutant, we have further confirmed the importance of constitutive activation of NF-κB by mutated *NOD2* for the pathogenesis of EOS/BS. We would like to emphasize the

FIG. 1 (**A**) Summary of the mutations identified in our patient. (**B**) NOD2 protein alignment among different species on the mutated amino acids. (**C**) NF-κB reporter assay using the *NOD2* deletion mutant. *In vitro* NF-κB reporter assays were performed as previously described [1, 3, 6, 7]. Mock vector, wild type *NOD2* (WT) and three *NOD2* variants (R334W, C495Y, H496L) derived from EOS/BS patients, were used as controls. Values represent the mean of normalized data (mock without MDP = 1) of triplicate cultures, and error bars indicate S.D. Shown is one representative result of three independent experiments. Protein expression levels of *NOD2* mutants analysed by western blotting are shown in the bottom panel.



usefulness of the NF-κB reporter assay with mutant *NOD2* for observing its role in EOS/BS, although the MAP kinase activation pathway and other possible pathways need to be evaluated to more completely understand the pathogenesis of the *NOD2* mutation in EOS/BS.

We have identified the first deletion mutation in the *NOD2* gene responsible for EOS/BS, and the mutant showed constitutive activation of NF-κB, which is one of the key features that lead to the pathogenesis of EOS/BS.

Rheumatology key message

- A six-base deletion in *NOD2* gene causes EOS.

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References

1 Rosé CD, Wouters CH, Meiorin S *et al.* Pediatric granulomatous arthritis: an international registry. Arthritis Rheum 2006;54:3337–44.

2 Aróstegui JI, Arnal C, Merino R *et al. NOD2* gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. Arthritis Rheum 2007;56:3805–13.

3 Okafuji I, Nishikomori R, Kanazawa N *et al.* Role of the *NOD2* genotype in the clinical phenotype of Blau syndrome and Early-onset sarcoidosis. Arthritis Rheum 2009;60:242–50.

4 Kanazawa N, Okafuji I, Kambe N *et al.* Early-onset sarcoidosis and *CARD15* mutations with constitutive nuclear factor κB activation: common genetic etiology with Blau syndrome. Blood 2005;105:1195–97.

5 Rosé CD, Doyle TM, McIlvain-Simpson G *et al.* Blau syndrome mutation of *CARD15/NOD2* in sporadic early onset granulomatous arthritis. J Rheumatol 2005;32:373–5.

6 Chamaillard M, Philpott D, Girardin SE *et al.* Gene-environment interaction modulated by allelic heterogeneity in inflammatory diseases. Proc Natl Acad Sci USA 2003;100:3455–60.

7 Becker ML, Rosé CD. Blau syndrome and related genetic disorders causing childhood arthritis. Curr Rheumatol Rep 2005;7:427–33.

8 Kambe N, Nishikomori R, Kanazawa N. The cytosolic pattern-recognition receptor NOD2 and inflammatory granulomatous disorders. J Dermatol Sci 2005;39:71–80.

9 Hsu YM, Zhang Y, You Y *et al.* The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. Nat Immunol 2007;8:198–205.

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Comment on: Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate

Sir, We read with interest the recent article by Amital *et al.* [1] that compared hepatotoxicity rates in PsA and RA patients treated with MTX based on the evaluation of standard liver function tests. The authors conclude that the incidence of hepatotoxicity does not differ between the two disease groups after adjusting for the cumulative dose of MTX.

Several studies in MTX-treated psoriasis patients have reported that isolated abnormalities of liver enzymes (i.e. alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) were poor predictors of the severity of liver histopathology. The authors state that the combined sensitivity of aspartate aminotransferase, alanine aminotransferase and bilirubin for detecting an abnormal liver biopsy has been rated at 0.86 based on a previous study [2]. This figure implies that 14% of those with normal liver function tests will have undetected hepatic disease. Larger studies have suggested that 30–50% of the psoriasis patients on MTX have normal standard liver function test results despite histology showing fibrosis and cirrhosis [3]. The lack of correlation between liver enzymes and hepatic fibrosis and cirrhosis has been the major factor leading to the recommendation that liver biopsies be done to monitor potential hepatotoxicity. In this study, the liver function tests were performed with varying frequency which could allow abnormal liver function tests to be missed. The authors acknowledge that the rates of other hepatotoxic agents such as alcohol use and the occurrence of other hepatic comorbidities were not known. We believe that these are significant confounding variables, which make the interpretation of the results of this study difficult. The British Association of Dermatologists recommends serial monitoring

PEDIATRIC RHEUMATOLOGY

CASE REPORT Open Access

Effect of anakinra on arthropathy in CINCA/NOMID syndrome

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Abstract

CINCA/NOMID is an autoinflammatory disorder characterized by the triad of neonatal onset of cutaneous symptoms, chronic meningitis, and recurrent fever and it presents with distinctive osteoarthropathy, synovitis mainly of the large joints and overgrowth of epimetaphyseal cartilage, particularly of the long bones. The cartilage overgrowth eventually causes osseous overgrowth and deformity that persists beyond skeletal maturity and leads to limb length discrepancy, joint contracture, and early degenerative arthropathy. Autoinflammation in CAPS/NOMID has been proven to derive from excessive release of interleukin-1 (IL-1). It has been well documented that the IL-1 receptor antagonist anakinra (Kineret(R)) helps mitigate systemic inflammation in the disorder. However, a general consensus has not been reached on its beneficial effect on osteoarthropathy. The case of a girl with CINCA/NOMID syndrome who showed dramatic improvement of osteoarthropathy after anakinra treatment is reported. A 4-year-old girl suffered at the age of 10 months from a generalized urticarial skin lesion with recurrent episodes of fever and growth disorder. Blood examination revealed persistent massive neutrophilia, anemia and intense acute phase response. She manifested knee joint swelling with limited ROM when she was 20 months old and was diagnosed as being CINCA/NOMID based on characteristic findings of radiograph despite negative CIAS1 mutation. Radiological examination demonstrated metaphyseal fraying and cupping and widening of the growth plate in the distal femur. MR imaging showed mottled gadolinium enhancement at the chondrosseous junction. Neither significant joint effusion nor synovitis was identified. At 2 years and 7 months of age, anakinra, 2 mg/kg/day given by regular daily subcutaneous injections, was started. A few days after the initiation of the treatment, her clinical symptoms and laboratory findings of active inflammation were promptly alleviated. She was not able to walk unaided prior to the treatment, but she walked independently 1 month after the treatment. Follow-up radiographs and MR imaging showed that growth plate widening and gadolinium enhancement at the chondrosseous junction were less conspicuous. Furthermore, longitudinal growth of the femur and tibia was identified during 20 months of observation.

Background

CINCA/NOMID is an autoinflammatory disorder characterized by the triad of neonatal onset of cutaneous symptoms, chronic meningitis, and recurrent fever [1-4] Since many cases are attributed to heterozygous gain-of-function mutations in *NLRP3 (CAIS1)*, the gene encoding cryopyrin [5,6], it is classified into cryopyrin-associated periodic syndromes (CAPS). CAPS include three allelic variants, ranging in order of increasing severity from Familial Cold Auto-inflammatory Syndrome (FCAS), previously termed Familial Cold Urticaria, through Muckle-Wells Syndrome (MWS) to Chronic Infantile Neurologic Cutaneous Articular Syndrome or Neonatal-Onset Multisystem Inflammatory Disease (CINCA/NOMID) [7,8]. However, CINCA/NOMID may be heterogeneous, and only 60% of affected individuals have *NLRP3* mutations.

CINCA/NOMID presents with distinctive osteoarthropathy, mainly of the large joints and overgrowth of epimetaphyseal cartilage, particularly of the long bones. Histological examination for overgrown cartilage shows complete disorganization of the cartilage cell columns and irregular metachromasia of the cartilage substance, but no inflammatory cell infiltrates [4]. The cartilage overgrowth eventually causes osseous overgrowth and deformity that persists beyond skeletal maturity and leads to limb length discrepancy, joint contracture, and early degenerative arthropathy [3,9,10] In particular,

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osteocartilaginous overgrowth in the patella and distal femur is so characteristic that its presence warrants a diagnosis of CINCA/NOMID.

Autoinflammation in CAPS has been proven to derive from excessive release of interleukin-1β (IL-1β) [11]. Interestingly, deficiency of the IL-1 receptor antagonist due to mutations of *IL1RN* gives rise to the phenotype sharing some features with CINCA/NOMID but with some clinical peculiarities regarding skin and bone manifestations [12]. It has been well documented that the IL-1 receptor antagonist anakinra (Kineret®) helps mitigate systemic inflammation in both disorders [12-14]. However, a general consensus has not been reached on its beneficial effect on osteoarthropathy. The case of a girl with CINCA/NOMID syndrome who showed dramatic improvement of overgrowth osteoarthropathy after anakinra treatment is reported.

Case presentation

The girl was born by normal vaginal delivery following an unremarkable pregnancy. The parents were healthy and nonconsanguineous. At 10 months of age, the girl presented with recurrent episodes of fever and growth disorder associated with a generalized, maculopapular, urticaria-like skin rash. Blood examination revealed massive neutrophilia, anemia, and intensely elevated acute phase reactants. Antibiotic treatment failed to alleviate the clinical symptoms. At 20 months of age, she developed knee joint swelling with limited ROM resulting in problems with standing and walking. Radiological examination demonstrated metaphyseal fraying and cupping and widening of the growth plate in the distal femur (Figure 1). MR imaging showed mottled gadolinium enhancement at the chondrosseous junction (Figure 2). Neither significant joint effusion nor synovitis was identified. She was diagnosed as having CINCA/NOMID on clinical and radiological grounds; however, analysis of cerebrospinal fluid (CSF) showed neither pleocytosis nor increased protein levels, and a molecular examination did not show *NARLP3* mutations. At 2 years and 7 months of age, anakinra, 2 mg/kg/day given by regular daily subcutaneous injections, was started. A few days after the initiation of the treatment, her constitutional symptoms, fever and urticaria-like rash, and acute-phase reactant levels were promptly alleviated. She was not able to walk unaided prior to the treatment, but she walked independently 1 month after the treatment. Follow-up radiographs and MR imaging (Figure 3) showed that growth plate widening and gadolinium enhancement at the chondrosseous junction were less conspicuous. Furthermore, longitudinal growth of the femur and tibia was identified during 20 months of observation (Data not shown).

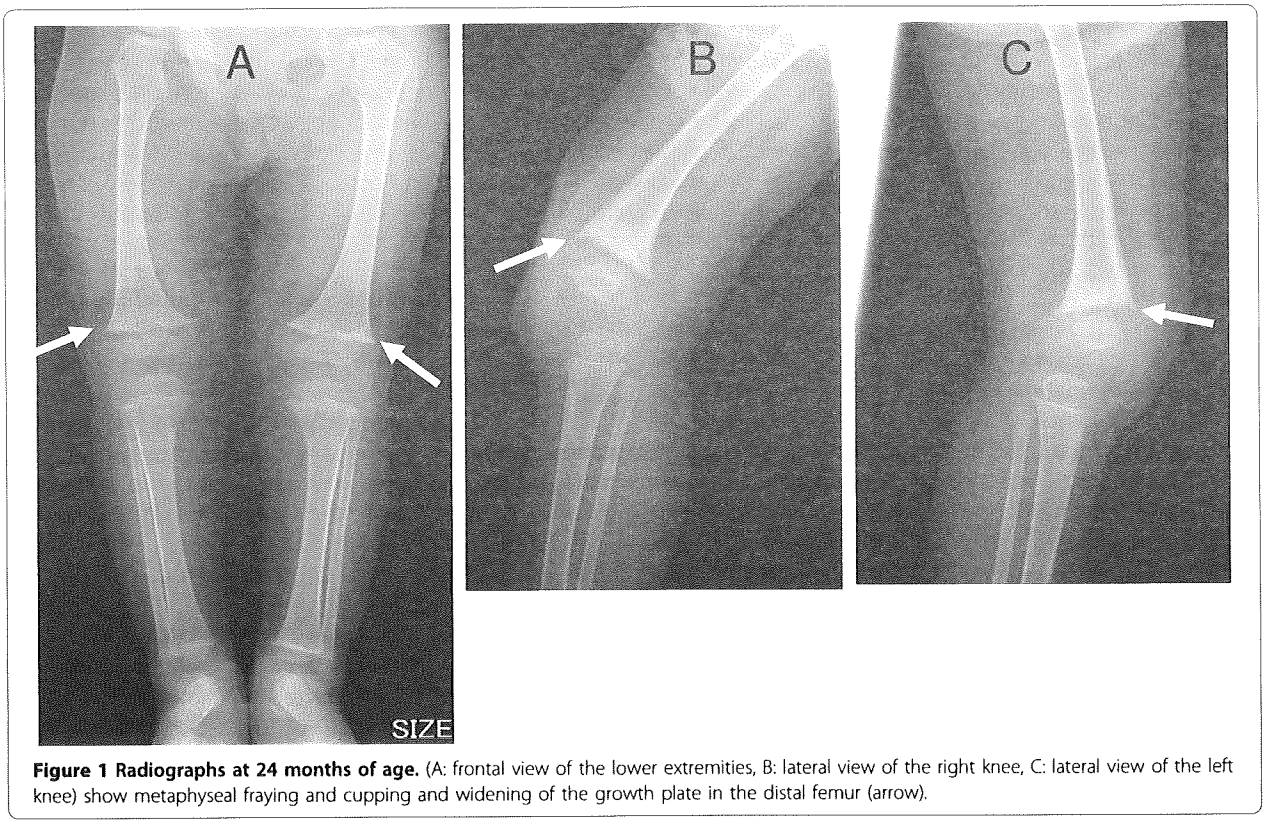

Figure 1 Radiographs at 24 months of age. (A: frontal view of the lower extremities, B: lateral view of the right knee, C: lateral view of the left knee) show metaphyseal fraying and cupping and widening of the growth plate in the distal femur (arrow).

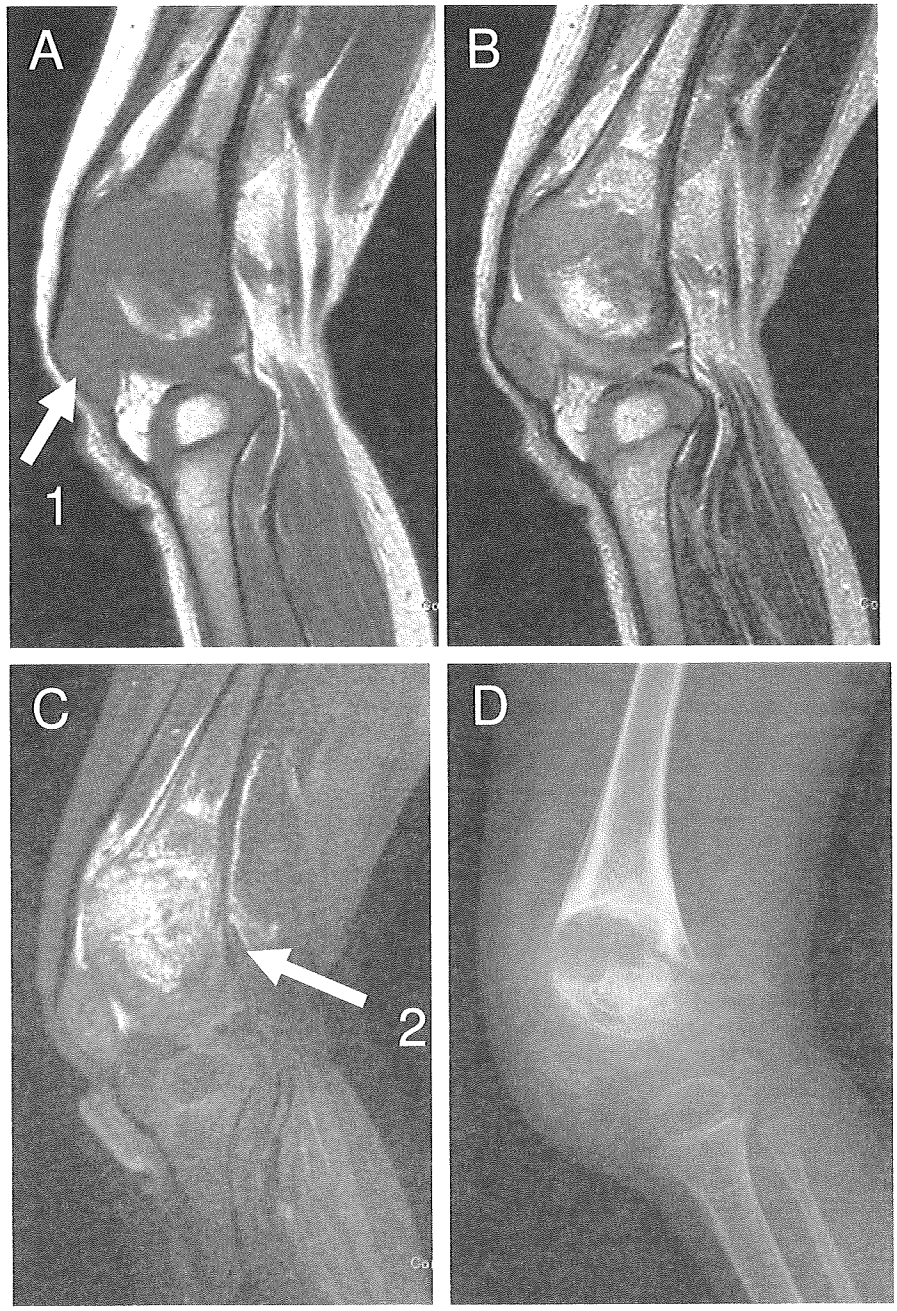

Figure 2 Sagittal MR images and lateral radiograph of the left knee at 2 years and 7 months of age, prior to introduction of anakinra. . (A: MRI T1-weighted, B: MRI T2-weighted, C MRI T1-weighted with fat suppression and gadolinium-enhancement, D radiograph): T1- and T2-weighted MR images show widening of the growth plate (arrow 1), and a gadolinium-enhanced MR image shows mottled enhancement at the chondroosseous junction (arrow 2).

Discussion

Although no *NARLP3* mutations were found in the present case, a diagnosis of CINCA/NOMID was warranted on clinical and radiological grounds. Her dermatological manifestation differed from that of deficiency of the IL-1 receptor antagonist (urticaria-like skin rash vs. pyoderma). Her clinical and radiological evolution following anakinra treatment implied that the therapy was effective not only in mitigating clinical symptoms of autoinflammation but also in preventing progression of osteoarthropathy. The beneficial effect of anakinra on arthropathy has been controversial.

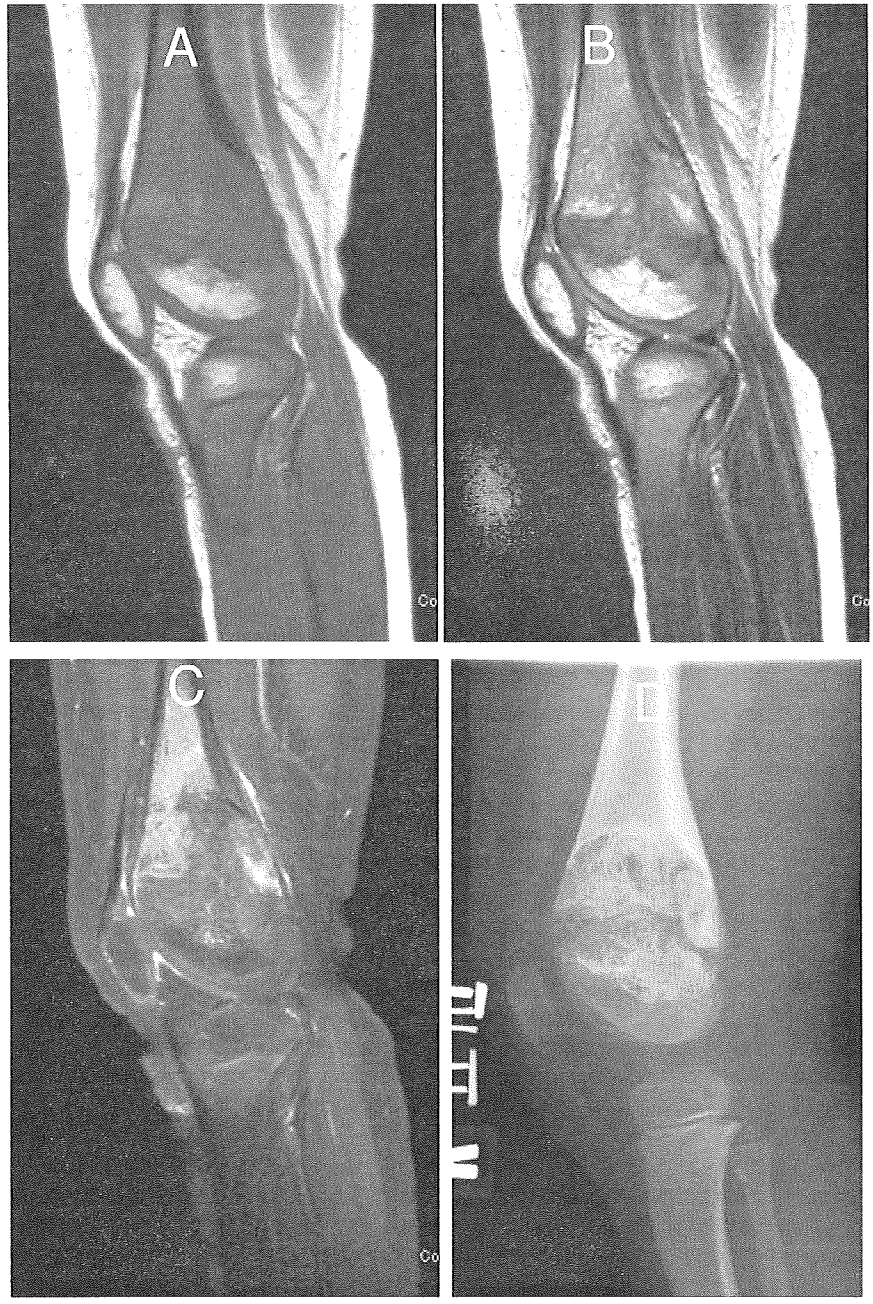

Figure 3 MR images and radiograph of the left knee at the age of 4 years and 3 months, after more than 20 months of anakinra treatment. (MRI A: T1-weighted, B: MRI T2-weighted, C: MRI T1-weighted with fat suppression and Ga enhancement, D radiograph). The growth plate widening previously seen (Figure 2) has alleviated with anakinra treatment. A gadolinium-enhanced MR image demonstrates less conspicuous enhancement at the chondroosseous junction after the anakinra treatment.

The case represented here indicated that the earlier anakinra was initiated, the better arthropathy was overcome. If the treatment had not been introduced, the osteoarthropathy eventually would have led to severe joint deformations, limb length discrepancy, and growth retardation, as previously reported. Once bone deformations develop in patients with CINCA/NOMID, they are very difficult to reverse [14]. However, the tragic consequences can be prevented by early medical intervention in this case.

The imaging findings in the present girl included widening of the growth plate and gadolinium enhancement at

the chondrosseous junction. These findings are in a broad sense termed "metaphyseal dysplasia", and are consistent with the known histological findings in CINCA/NOMID. According to a previous report, the histological findings for biopsy specimens from a "bony mass" were 1) disorganized cartilage at the growth plate and 2) thin metaphyseal trabeculae mixed with relatively acellular cartilage, fibrous tissues, and foci of calcification [10] The latter finding may correspond with gadolinium enhancement of the chondrosseous junction. In the present case, the anakinra treatment provided remodeling of the "metaphyseal dysplasia" with alleviation of gadolinium enhancement. This fact suggests that osteoarthropathy in CINCA/NOMID is caused by overproduction of IL-1β, as are the symptoms of autoinflammation and disappearance of them by specific receptor antagonist of IL-1β.

Osteoarthropathy is significant in approximately 60% of CINCA/NOMID patients, and it is more prevalent in cases with deficiency of the IL-1 receptor antagonist. The mechanism to explain why the excessive production of IL-1β causes distinctive osteocartilaginous overgrowth in CINCA/NOMID still remains unclear. Though it has been reported that IL-1β exerts inhibitory effects on murine ATDC5 chondrocyte dynamics and metatarsal longitudinal growth [15], recent observation suggested that overgrowth arthropathy in CINCA/NOMID is not driven by IL-1β, but such overgrowth may be due to abnormal apoptosis at the site of enchondral ossification as NALP3 is expressed in cartilage [16,17].

Conclusion

This report indicated the importance of earlier indication of anakinra for better outcome of arthropathy in CINCA/NOMID syndrome. Once once bone deformations develop in the patients, they are very difficult to reverse even with anakinra.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal.

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Authors' contributions

TM drafted the manuscript and participated in its design. MK, TK, RH, UK, TS and TI participated in drafting of the manuscript and participated in its design. YI and GN participated in the drafting of the manuscript and supplied the radiological images used for the manuscript. SY conceived of the case report, participated in drafting the manuscript and gave final approval for the version to be submitted for publication.

Competing interests

The authors declare that they have no competing interests.

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References

1. Prieur AM, Griscelli C: **Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation.** *J Pediatr* 1981, **99**:79-83.
2. Hassink SG, Goldsmith DP: **Neonatal onset multisystem inflammatory disease.** *Arthritis Rheum* 1983, **26**:668-673.
3. Torbiak RP, Dent PB, Cockshott WP: **NOMID-a neonatal syndrome of multisystem inflammation.** *Skeletal Radiol* 1989, **18**:359-364.
4. Prieur AM: **A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy.** *Clin Exp Rheum* 2001, **19**:103-106.
5. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J: **NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder.** *Immunity* 2004, **20**:319-325.
6. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD: **Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome.** *Nat Genet* 2001, **29**:301-5.
7. Aksentijevich I, D Putnam C, Remmers EF, Mueller JL, Le J, Kolodner RD, Moak Z, Chuang M, Austin F, Goldbach-Mansky R, Hoffman HM, Kastner DL: **The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model.** *Arthritis Rheum* 2007, **56**:1273-85.
8. Hull KM, Shoham N, Chae JJ, Aksentijevich I, Kastner DL: **The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations.** *Curr Opin Rheumatol* 2003, **15**:61-9.
9. Kaufman RA, Lovell DJ: **Infantile-onset multisystem inflammatory disease: radiologic findings.** *Radiology* 1986, **160**:741-746.
10. Hill SC, Namde M, Dwyer A, Poznanski A, Canna S, Goldbach-Mansky R: **Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA).** *Pediatr Radiol* 2007, **37**:145-52.
11. Dinarello CA: **Unraveling the NALP-3/IL-1β inflammasome: a big lesson from a small mutation.** *Immunity* 2004, **20**:243-6.
12. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, Laxer R, Tedgård U, Cowen EW, Pham TH, Booty M, Estes JD, Sandler NG, Plass N, Stone DL, Turner ML, Hill S, Butman JA, Schneider R, Babyn P, El-Shanti HI, Pope E, Barron K, Bing X, Laurence A, Lee CC, Chapelle D, Clarke GI, Ohson K, Nicholson M, Gadina M, Yang B, Korman BD, Gregersen PK, van Hagen PM, Hak AE, Huizing M, Rahman P, Douek DC, Remmers EF, Kastner DL, Goldbach-Mansky R: **An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist.** *N Engl J Med* 2009, **360**:2426-37.
13. Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, Kim HJ, Brewer C, Zalewski C, Wiggs E, Hill S, Turner ML, Karp BI, Aksentijevich I, Pucino F, Penzak SR, Haverkamp MH, Stein L, Adams BS, Moore TL, Fuhlbrigge RC, Shaham B, Jarvis JN, O'Neil K, Vehe RK, Beitz LO, Gardner G, Hannan WP, Warren RW, Horn W, Cole JL, Paul SM, Hawkins PN, Pham TH, Snyder C, Wesley RA, Hoffmann SC, Holland SM, Butman JA, Kastner DL: **Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition.** *N Engl J Med* 2006, **355**:581-92.
14. Neven B, Marvillet I, Terrada C, Ferster A, Boddaert N, Couloignier V, Pinto G, Pagnier A, Bodemer C, Bodaghi B, Tardieu M, Prieur AM, Quartier P: **Long term efficacy of the Interleukin-1 receptor antagonist anakinra in ten patients with Neonatal-onset multisystem inflammatory disease/ Chronic Infantile neurologic, cutaneous, articular syndrome.** *Arthritis Rheum* 2010, **62**:258-267.
15. MacRae VE, Farquharson C, Ahmed SF: **The restricted potential for recovery of growth plate chondrogenesis and longitudinal bone growth following exposure to pro-inflammatory cytokines.** *J Endocrinol* 2006, **189**:319-28.
16. eldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, Teillac-Hamel D, Fischer A, de Saint Basile G: **Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes.** *Am J Hum Genet* 2002, **71**:198-203.

17. McCall SH, Sahraei M, Young AB, Worley CS, Duncan JA, Ting JP, Marriott I: **Osteoblasts express NALP3, a nucleotide-binding domain and leucine-rich repeat region containing receptor implicated in bacterially induced cell death.** *J Bone Miner Res* 2008, **23**:30-40.

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ORIGINAL ARTICLE

Changing Prevalence and Severity of Childhood Allergic Diseases in Kyoto, Japan, from 1996 to 2006

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ABSTRACT

Background: Published data regarding changes in the prevalence of childhood allergic diseases in Japan have been limited.

Methods: To observe changes in the recent trends of the childhood allergy epidemic in Japan, a population-based questionnaire survey of allergic diseases was conducted among 13,215 schoolchildren, aged 7 to 15 years, in Kyoto, Japan in 2006. The results were compared with those obtained in the 1996 survey using the same scale and methods in the same region.

Results: The prevalences of bronchial asthma (BA), atopic dermatitis (AD), allergic rhinitis (AR), and allergic conjunctivitis (AC) in 1996 and 2006 were 5.1% and 5.0% ($p = 0.58$), 4.2% and 5.6% ($p < 0.0001$), 20.3% and 27.4% ($p < 0.0001$), and 13.3% and 25.2% ($p < 0.0001$), respectively. Although the distribution of BA severity improved, the severity distribution of AD, AR, and AC all deteriorated. The lifetime prevalence (present prevalence and past history combined) of BA increased from 6.5% to 7.6% ($p < 0.0001$). The sex ratio analysis showed that the female predominance in the prevalence of AD observed in 1996 disappeared in 2006, indicating a particular rise in AD prevalence among boys.

Conclusions: Overall, the results indicate that the rising trend of allergic diseases, especially in AD, AR, and AC, continues among schoolchildren living in Kyoto, Japan. Special attention should be paid to skin and naso-ocular symptoms.

KEY WORDS

allergic disease, epidemiology, prevalence, questionnaire, schoolchildren

INTRODUCTION

The prevalence of childhood allergic diseases has increased over the last few decades and has become a significant social and public health problem, especially in industrialized countries.[1] However, recent continuing trends which show an increased prevalence might be misinterpreted due to changes in diagnostic labeling, heightened awareness of the problem, and the presence of selection or information bias in previous studies.[2] Thus, in order to accurately evaluate the recent trends in the childhood allergy epidemic, it is crucial to repeatedly compare sequential data using identical, simple, validated questionnaires involving children of the same age and region sampled in the same way.[3] Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) was performed for this purpose between 1999 and 2004 (mostly 2002-03),[4] and there are abundant data comparing the results with those of the Phase I ISAAC study between 1992 and 1998 (mostly 1994-95). The data included mixed results, with some studies showing an increased prevalence,[5-7] while others showed trends that plateaued or decreased.[1,8-10] There was also a variation in the trend for prevalence depending on the kind of disease, as well as geographical differences.[2,11-16]

In Japan, there have been very few published data regarding the prevalence of childhood allergic diseases over time, with one set of data showing an in-

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