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Aspirin is an Enhancing Factor for Food-dependent Exercise-induced Anaphylaxis in Children

Running head: Aspirin enhances FDEIA in children

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INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA) is typified by the onset of anaphylaxis during or soon after exercise preceded by the ingestion of a causal food. In Japan, a questionnaire-based prevalence study of 76,247 junior high-school students revealed an FDEIA prevalence of 0.017%. ¹ Physical activity is beneficial for children, with positive outcomes pertaining to both mental and physical well-being. When patients, particularly paediatric patients, are suspected of having FDEIA, low physical activity owing to restricted exercise reduces their quality of life (QOL). The confirmation of FDEIA can be challenging. Although a diagnosis of FDEIA is important, challenge tests performed in the hospital regarding food and exercise are often negative, even in patients with a clear history of FDEIA.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to enhance FDEIA symptoms. ^{2,3} In addition, aspirin reportedly enhances the symptoms of food allergies even without exercise in adults, ⁴ and a few reports have shown that aspirin enhances both FDEIA and food allergy symptoms without exercise in children. ⁵ The aim of the present study was to determine the effect of aspirin on challenge tests for FDEIA and food allergies with or without exercise in children suspected of having FDEIA based on their medical histories.

METHODS

Fifty-one children (38 males and 13 females, 4–16-year old and median age: 11 years) suspected of having FDEIA were recruited from the outpatient clinic of the Department of Pediatrics at Fukuoka National Hospital between 2006 and 2015. Patients over 18 years of age were excluded from the study sample, as were subjects who showed allergic symptoms to the same amount of causal food used in the challenge without exercise. No patients had a history of drug allergies, particularly allergy to

NSAIDs. Anaphylaxis was defined as a serious allergic response that often involves swelling, hives, wheezing and typically more than one system of the body. All patients had experienced more than a single episode of anaphylaxis after exercise. Patient clinical histories and characteristics are shown in the Table. Parental written consent was obtained for each child, and the Fukuoka Hospital Ethics Board approved the study (the ethics approval No. F24-19).

The entire study took place over 3 days (Fig.). Patients were instructed to discontinue using antihistamine drugs to manage their allergies 3–7 days before the challenge according to the type of antihistamine. The exercise challenge commenced 30 min after food ingestion and was standardized as 30 min of aerobic exercise followed by 6 min of anaerobic exercise to induce a heart rate of at least 80% of the child's maximum predicted heart rate ($220 - \text{age}$). The heart rate was monitored throughout the exercise. On the first day, the patient underwent a causal food and exercise challenge using an ergometer or treadmill. The patient then underwent an aspirin and causal food challenge on the second day and an aspirin, causal food and exercise challenge on the third day. Aspirin (10 mg/kg and maximum: 500 mg) was administered 30 min before food intake. The patient's history, results of specific IgE levels and skin-prick testing (SPT) determined causal food. For the wheat challenge, noodles made from wheat flour (70 g) and a small amount of salt were used. For the shrimp challenge, boiled shrimp (50 g) was prepared. The other food amounts were determined based on each patient's history and whether anaphylaxis had occurred. The outcomes were recorded as objective symptoms (urticaria, cough, dyspnoea, oedema, nausea, vomiting and shock). We defined positive results as those in which patients expressed any one symptom such as urticaria. If a severe reaction occurred, the challenge test was stopped and the patient was immediately treated with antihistamines or adrenaline.

Skin-prick testing (SPT) was performed using commercial food extracts (Torii Pharmaceutical, Tokyo, Japan) or with fresh peach, orange or onion using prick lancets (AB Nordic Medifield, Stockholm, Sweden). The reactions were read as the longest length $\times$ the perpendicular wheal length at 15 min. The responses were then compared with those observed in the positive histamine (10 mg/mL) and negative physiologic saline controls. The wheal size observed in the histamine-positive control was evaluated as the ratio of the allergen divided by the histamine level. The first SPT was performed on day 1. The same tester then performed a second SPT at 30 min after aspirin intake on day 2.

Specific IgE levels in response to the causal foods were determined using the ImmunoCAP/fluoro-enzyme immunoassay kit (Pharmacia, Uppsala, Sweden). Specific IgE levels of 0.35 kUA/L or greater were defined as a positive result.

For the statistical analysis, we used the McNemar's test to compare the results of the challenge test according to aspirin pretreatment.

RESULTS

Allergic reactions were successfully challenged in 26 patients (6 females and 22 males, age range: 6–16 years and median age: 13.1 years). The symptoms of the 26 positive-challenged cases were urticaria in 21 cases (81%), coughing and wheeze in 14 cases (54%), angioedema in 7 cases (27%), shock in 3 cases (12%) and nausea and vomiting in 2 cases (8%), as shown in the table. One patient experienced wheezing only following the challenge with shrimp and exercise on day 1 (Case No.8). On the remaining 2 days, he was only challenged with exercise enabling us to exclude exercise-induced bronchoconstriction. The foods responsible for positive responses in the patients with FDEIA included shrimp in 9 patients (35%), wheat in 7 patients (27%), milk in 4

patients (15%) and others in 6 patients (peach in 2 patients and orange, sesame, onion and fish in 1 patient each; 23%).

Allergic reactions were induced by the food and exercise challenge in 14 (54%) of the 26 positive patients. The combination of aspirin and food (shrimp or orange) without exercise induced an allergic reaction in 2 (14%) of the 14 patients. However, when the aspirin pretreatment was followed by a food and exercise challenge, all 26 patients exhibited symptoms. There was a significant difference in the positive rates of the tests when pretreated with and without aspirin ($p < 0.01$).

Specific IgE antibodies against causative food allergens were detected in 20 (77%) of the 26 patients with positive results from the 3-day food and exercise challenge tests. Positive SPTs using the causative food allergens were detected in 25 (96%) out of 26 cases. Only 1 case with suspected wheat-triggered FDEIA had negative results for both tests. The SPTs using the causative food allergens were enhanced after aspirin pretreatment in 7 (64%) of 11 patients. Of the 2 patients with aspirin-induced FDEIA symptoms in response to food intake without exercise, 1 showed enhanced SPT results (Case No. 23).

DISCUSSION

In 14 of the 26 (54%) patients with positive responses, the combination of food and exercise induced allergic symptoms. These results are similar to a report of FDEIA cases in Japan that included adults (average age, 34 years), wherein 14 out of 31 patients (45%) exhibited positive results.⁶ Furthermore, aspirin induced positive results in 14 patients with negative or mild symptoms after a challenge with food and exercise only. Thus, the addition of aspirin increased the severity and frequency of allergic reactions

during challenges with a causal food and exercise in paediatric patients with suspected FDEIA.

Several mechanisms for the enhancement of the allergic reaction by aspirin have been proposed. A mechanism by which exercise enhances FDEIA is the facilitation of allergen absorption from the gastrointestinal tract.⁷ Reportedly, wheat is the most common specific food allergen responsible for inducing FDEIA, particularly in adults.⁶ Indeed, wheat-dependent exercise-induced anaphylaxis is the best-studied model of FDEIA.^{3,7} Increased blood levels of gliadin are reportedly correlated with clinical symptoms induced by exercise, and aspirin has been found to induce anaphylaxis in patients with wheat-dependent exercise-induced anaphylaxis.⁸

In this study, only two patients had a reaction to aspirin and food without exercise. Izumi et al. reported that 12 (52.1%) of 23 patients with FDEIA (average age, 34 years) exhibited food-induced reactions after treatment with NSAIDs but without an exercise challenge.⁶ The potential mechanism underlying FDEIA may be explained by gut resistance against NSAIDs. It was reported that infant but not adult rats demonstrated resistance to the ulcerogenic effects of indomethacin.⁹ There is no report on the difference of the effect of NSAID in the intestine between adults and children *in vivo*. As the function of the intestine matures, aspirin

may affect absorption in the intestine without exercise. Aspirin in combination with exercise enhanced food absorption in the intestine in almost all child FDEIA cases.

The anti-inflammatory actions of aspirin have been primarily attributed to the inhibition of prostaglandin synthesis. One key feature of aspirin intolerance is the independent inhibition of COX that results in the overproduction of cysteinyl leukotrienes, in which mast cells have been implicated. Suzuki et al. reported another potential mechanism for the secretion of the cysteinyl leukotriene, LTC₄, in IgE-dependent mast cells and its modulation by aspirin, placing special emphasis on the role

of Ca²⁺ signals.¹⁰ In this study, we used a positive ratio calculated from the histamine controls to evaluate SPTs using causative food allergens. Increased histamine skin reactivity over time is associated with an increase in positive allergen SPT; hence, the histamine controls are necessary to correctly evaluate the enhancement of allergen SPTs following aspirin treatment. When allergen SPTs with histamine controls were used to judge the effect of aspirin, an enhanced response was observed in 7 (64%) of the 11 paediatric patients. SPT reaction to causative food allergens was enhanced by pretreatment with oral aspirin, suggesting that aspirin accelerates histamine release from mast cells to a specific allergen.³ Thus, the modulation of mast cell activity through aspirin might be a potential mechanism by which aspirin influences FDEIA in children.

In the present study, specific IgE levels were negative in 6 (23%) of the 26 subjects with positive challenge results. In contrast, SPTs using causative food allergens were positive for 23 (96%) of the 24 subjects with positive responses to the challenge tests. Only 1 case with suspected wheat-triggered FDEIA had negative results for both tests. There were 12 negative SPTs in 25 patients with negative responses to the challenge tests. This result means that aspirin and exercise cannot enhance IgE-mediated reactions without positive SPT or IgE in almost all paediatric patients. In adult FDEIA cases, 15.6% of patients were reported to have negative results for both tests.⁶ Negative SPT is a useful marker for denying FDEIA in children with suspected FDEIA.

There were more males who participated in this study. Aihara has already reported that FDEIA frequency is significantly higher in boys than in girls.¹ This difference may reflect in part that a certain level of exercise strength is required to induce FDEIA. In Japan, boys tend to prefer more active sports than girls. However, we do not have any results which explain this difference in gender for FDEIA.

There are limitations of this study as follows. The sequential study design means that a 'carryover' effect cannot be excluded as a possible reason why more patients with FDEIA reacted on the third food challenge compared to the second one. The lack of reactions on the second food challenge might be explained by this. The patients and assessors were not blind to the challenge conditions, which of course would not be easily feasible. This could bias interpretation of the challenge outcome. Robust criteria are required for determining the challenge outcome, similar to the PRACTALL criteria. There was no 'food challenge' without exercise or aspirin. In addition, we did not include an extra day to confirm the diagnosis of an aspirin allergy or cholinergic urticaria, which would have added further strength and detail to the findings, although it may not have been logistically feasible. Because aspirin can induce positive results without exercise, its administration is likely to be responsible for false-positive results for FDEIA. When we performed the aspirin, food and exercise challenge in aspirin and food positive patient (Case No.3), He showed severe allergic reactions. Therefore, we discontinued the aspirin, food and exercise challenge and diagnosed aspirin and food positive patients as FDEIA. Our study was a single centre study conducted only in the Japanese population. Regarding the effect of aspirin, Brockow et.al reported that aspirin was an enhancing factor of FDEIA in a non-Japanese population.⁸

In conclusion, aspirin enhanced the frequency of positive reactions during challenges with causal food and exercise by 2 fold. In children with suspected FDEIA where food and exercise challenges fail to provoke symptoms, the addition of aspirin to the challenge protocol is a useful step that can reduce the rate of false negative challenge findings. Aspirin may be considered for selective addition to only negative and mild symptom cases because of food and exercise challenges, not to all cases. Aspirin and food challenges do not seem to be necessary for all FDEIA paediatric patients. After 1 patient developed an anaphylactic reaction, we discontinued the following aspirin, food and exercise challenge (Case No.23). For safety reasons, it is better to perform the aspirin and food challenge in children. Exercise may be an indispensable factor of the aspirin-induced enhancement of food allergies for children and not adults. Further study is needed to elucidate the mechanism by which FDEIA occurs in paediatric patients.

Acknowledgement and conflicts of interest

We thank the children and parents who participated in this study. There are no conflicts of interest to declare.

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Fig. Study protocol. Exercise challenge: 30 min of aerobic exercise followed by 6 min of anaerobic exercise to induce a heart rate of at least 80% of the child's maximum predicted heart rate (220-age). Aspirin: 10 mg/kg (maximum, 500 mg). Food amounts (protein; g): Boiled shrimp 50 (9.2), Noodles 200 (16), Cow's milk 200 (6.6), based on each patient's history and whether anaphylaxis had occurred.

Table. Results of positive provocation of 26 cases of food dependent exercise induced anaphylaxis

No.	History of FA	Causal food	Immunological studies				Challenge testing				
			Specific IgE	SPT*	SPT*+A	EN	Protein	F+E	A+F	A+F+E	
			(kUA/L)	/Histamine	/Histamine		(total dose)				
(g)											
1	-	Shrimp	6.85	3.0/3.0	2.0/6.0	-	9.2(50)	N	N	U,W	
2	-	Shrimp	0.53	2.2/2.0	-		5.5(30)	Conj,U	-	-	
3	-	Shrimp	35.5	-	-		9.2(50)	U	U	U,V,H	
4	-	Shrimp	31.2	8.0/5.0	5.5/5.0	-	9.2(50)	N	N	U	
5	-	Shrimp	4.16	5.0/5.0	7.0/4.0	+	9.2(50)	N	N	AE,W,H	
6	-	Shrimp	<0.35	3.5/4.5	4.5/3.0	+	18.4(100)	U,W	N	-	
7	-	Shrimp	<0.35	6.5/4.0	-		9.2(50)	U	-	-	
8	-	Shrimp	58.2	-	-		9.2(50)	W	-	-	
9	Shrimp(s)	Shrimp	20.9	3.0/3.5	-		14.7(80)	U,AE,W	-	-	
		Wheat	ω5gliadin								
10	-	Wheat	<0.35	<0.35	2.0/1.5	-	16(200)	U,W	-	-	
11	-	Wheat	0.44	0.81	2.5/2.0	2.0/5.0	-	16(200)	N	N	U
12	Egg	Wheat	<0.35	<0.35	6.0/5.0	2.0/2.0	-	16(200)	N	-	U
13	-	Wheat	4.75	22.2	4.0/4.5	-	16(200)	AE,W	-	-	

14	-	Wheat	1.01	<0.35	4.0/4.0	3.0/2.0	+	16(200)	N	N	U
15	-	Wheat	<0.35	<0.35	1.0/4.0	-		16(200)	N	N	U,AE
16	Fruits	Wheat	2.29	<0.35	3.5/4.5	-		16(200)	AE,W	N	-
17	Milk(post IT)	Milk		37	1.5/1.0	-		6.6(200)	U	-	-
18	-	Milk		1.51	6.0/6.5	--		6.6(200)	N	N	U,W
19	-	Milk		0.61	4.0/5.0	7.5/5.0	+	13.2(400)	N	N	U
20	Milk	Milk		10.9	4.5/2.5	-		9.9(300)	U	-	U,H
21	Peach	Peach		<0.35	2.5/5.0	-		0.75(150)	U,V	N	-
22	-	Peach		3.39	10.0/2.0	-		1.13(225)	U,W	-	-
23	-	Orange		0.85	4.5/6.5	4.5/2.0	+	0.45(45)	N	U,AE,W	-
24	-	Tuna		19.8	7.5/5.0	-		21.1(80)	U,W	-	-
25	-	Sesame		3.71	10.0/6.5	9.0/3.5	+	0.41(2)	N	-	U,W
26	-	Onion		1.4	1.0/4.5	3.5/3.0	+	0.5(50)	N	N	AE,W

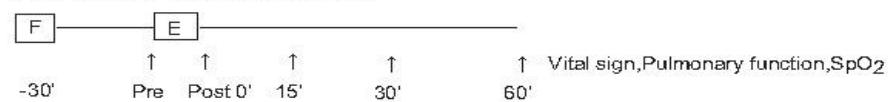
FA:food allergy, A:aspirin, F:food,E:exercise,Conj:conjunctivitis,U:urticaria,W: wheeze / cough, N: no symptom, V: vomiting/nausea,

H;Hypotension, AE:angioedema, S:strange mouth sensation, EN:enhancement by aspirin, IT:Immunotherapy

*Average wheal diameter in millimeters

There was significant difference in the positive rates of the tests when pretreated with aspirin and without (p <0.01) by McNemar's Test.

Day 1: Food(F) +Exercise(E) challenge



Day 2: Aspirin(A)+Food(F) challenge



Day 3: Aspirin(A)+Food(F) +Exercise(E) challenge

