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Early Allergic Sensitizations and Their Relevance to Atopic Diseases in Children Aged 6 Years: Results of the GINI Study

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Abstract

Background: Only a few studies have analyzed the value of early sensitization in predicting the development of atopic disease. The relevance of low immunoglobulin (Ig) E antibody levels in this respect also remains unclear.
Objective: To investigate the relevance of sensitization in 12-month-old children in the development of atopic disease by the age of 6 years.
Methods: We analyzed data for 1290 children with a positive family history of atopy from the prospective, multicenter German Infant Nutritional Intervention (GINIplus) study and investigated the relationship between the presence of detectable specific IgE antibodies at the age of 12 months and the development of atopic disease by the age of 6 years.
Results: In all, 10.9 % of children analyzed developed sensitization. At the age of 6 years, 20.6% of children with early sensitization had eczema compared to 9.4% of those without (odds ratio [OR], 2.31; 95% confidence interval [CI], 1.42-3.74). The corresponding figures were 15.4% vs 7.3% for allergic rhinitis (OR, 2.22; CI, 1.31-3.78) and 10.2% vs 2.6% (OR, 3.93; 95% CI, 1.98-7.76) for asthma. Children with early sensitization to aeroallergens had the greatest risk of subsequent atopic disease. Early sensitization did not increase risk in children without eczema within the first year of life. Very low specific IgE levels (0.18-0.34 kU/L) were not significantly associated with any of the outcomes analyzed.
Conclusion: Sensitization to common food allergens and to aeroallergens in particular during the first year of life was found to be a strong predictor for the development of atopic disease by the age of 6 years in children with a positive family history of atopy.

Key words: Atopic disease. Children. GINI study. Low immunoglobulin E (IgE) levels. Sensitization.

Resumen

Antecedentes: Solamente unos pocos estudios han analizado el valor de la sensibilización temprana en la predicción del desarrollo de la enfermedad atópica. La relevancia de los niveles bajos de inmunoglobulina (Ig) E a este respecto tampoco está clara.
Objetivo: Investigar la relevancia de la sensibilización en niños de 12 meses de edad en el desarrollo de la enfermedad atópica a la edad de 6 años.
Métodos: Analizamos los datos de 1290 niños con historia familiar positiva de atopia del estudio prospectivo, multicéntrico "intervención nutricional de niños alemanes" (GINIplus) y se investigó la relación entre la presencia de anticuerpos IgE específcos detectables a la edad de 12 meses y en el desarrollo de enfermedad atópica a la edad de 6 años.
Resultados: 10,9 % de los niños analizados desarrollaron sensibilización. A la edad de 6 años, el 20,6% de los niños con sensibilización temprana tenían eczema comparado con el 9,4% de los que no tenían sensibilización (odds ratio [OR], 2,31; intervalo de confianza al

95% [IC], 1,42-3,74). Las cifras correspondientes fueron 15,4% vs 7,3% para la rinitis alérgica (OR, 2,22; IC 95%, 1,31-3,78) y 10,2% vs 2,6% (OR, 3,93; IC 95%, 1,98-7,76) para asma. Los niños con sensibilización temprana a aeroalérgenos presentaron el mayor riesgo de una posterior enfermedad atópica. La sensibilización temprana no incrementó el riesgo de los niños sin eczema en el primer año de vida. Los niveles muy bajos de IgE específica (0,18-0,34 kU/L) no se asociaron con ninguno de los resultados analizados.
Conclusión: La sensibilización a los alérgenos alimentarios comunes y aeroalérgenos en particular, durante el primer año de vida, se ha observado que es un fuerte predictor para el desarrollo de enfermedad atópica a la edad de 6 años en niños con historia familiar positiva de atopia.

Palabras clave: Enfermedad atópica. Niños. Estudio de Intervención Nutricional de Niños Alemanes (GINI). Niveles bajos de IgE. Sensibilización.

Introduction

The prevalence of atopic diseases has increased in recent years [1] and it remains a matter of controversy whether primary preventive measures, such as house dust mite eradication and avoidance of food allergens, can prevent the development of allergic sensitization and atopic diseases in children with a family history of atopy [2-7].

There are only a few birth cohorts for which specific immunoglobulin (Ig) E antibody levels and skin prick test results are available for the first year of life [8]. While it is well known that children with atopic diseases often exhibit sensitization, the ability of sensitization to predict the subsequent development of atopic disease is less clear.

We investigated the association between early sensitization and the prevalence of atopic disease in children aged 6 years. The children all had a positive family history of atopy and were part of a large multicenter birth cohort.

Material and Methods

We analyzed data for children up to 6 years of age from the German Infant Nutritional Intervention (GINI) study, a multicenter, double-blind, randomized intervention study which has been described previously [6,9]. In brief, from 1995 to 1998, 5991 newborn children were recruited into the GINIplus study from 2 areas of Germany, Munich and Wesel; 2252 of these children, all with a positive family history of atopic disease, were enrolled into the GINI study, designed primarily to examine the preventive effect of different hydrolyzed infant formulas on the development of atopic diseases.

Families participating in the GINI group were invited to clinical examinations when the children were 1, 4, 6, 8, 12, and 36 months of age and questionnaires were filled in by parents when the children were 1, 2, 3, 4, and 6 years old.

At 12 months, specific IgE antibodies against cow milk proteins (f76, f77, f78), egg, soy allergen, cat allergen, house dust mites, timothy grass, and birch pollen (f1, f14, e1, d1, d2, g6, t3) (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden) were measured. Sensitization was defined at a level of ≥0.35 kU/L (radioallergosorbent test [RAST] class ≥1). Low sensitization was defined as an IgE level of between 0.18 and 0.34 kU/L (RAST class 0.5).

Atopic disease was defined when a parent reported a physician's diagnosis of eczema, asthma, or allergic rhinitis in the 12 months prior to their child turning 6 years. For eczema, we included a definition of eczema at 6 years only, excluding children with a physician's diagnosis of eczema within the first year of life.

A positive family history of atopy was defined as single when heredity for atopy was observed in 1 parent and/or biological sibling, and as double, when it was observed in both parents. Parental education (evaluated in the parent who had attended school for longest) was categorized as low (elementary school/no qualification), medium (secondary school) and high (at least German high school graduation). Written informed consent was obtained from both parents and the study was approved by the local ethics committees.

Analyses were restricted to children with RAST results at the age of 1 year and a completed questionnaire at 6 years.

Statistical Analysis

$\chi 2$ tests were used for univariate analysis and multiple logistic regression analyses were used to examine associations between early sensitization and the presence of atopic disease at the age of 6 years. All models were adjusted for a priori defined potential confounding factors such as family history of atopic disease, parental education, siblings, gender, study region, and type of milk feeding during the first 4 months of life. Results are presented as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). A *P* value of less than .05 was considered statistically significant. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 2252 children recruited for the GINI study, 1680 (74.6%) had a completed questionnaire at 6 years and 1492 had RAST results for the age of 12 months. Both of these test results were available for 1290 children. Table 1 shows the characteristics of the children included in our analyses. We also examined children according to their participation in the RAST

and questionnaire. A positive RAST (≥0.35 kU/L) at 12 months, sex, or family history of atopic disease had no influence on participation in the questionnaire at 6 years. Parents with a higher level of education and fewer children filled in the questionnaire significantly more often than did other parents. There was no difference in the RAST participation rate between children with or without atopic disease at a later age (data not shown).

Table 1. Characteristics of Study Population

		No./Total (%)
Study region	Munich	765/1290 (59.3)
	Wesel	525/1290 (40.7)
Sex	Male	679/1290 (52.6)
	Female	611/1290 (47.4)
Family history of atopy	Single	893/1290 (69.2)
	Double	397/1290 (30.8)
Siblings	0	762/1283 (59.4)
	1	391/1283 (30.5)
	>1	130/1283 (10.1)
Parental education	Low	71/1286 (5.5)
	Medium	349/1286 (27.1)
	High	866/1286 (67.3)
Positive RAST[a]	Any allergen	140/1290 (10.9)
	Any food allergen	125/1278 (9.8)
	Any aeroallergen	29/1288 (2.3)
Positive RAST 0.5[b]	Any allergen	17/1059 (1.6)
Atopic disease	Eczema at 6 years	133/1253 (10.6)
	Eczema at 6 years only[c]	80/1166 (6.9)
	Allergic rhinitis at 6 years	102/1253 (8.1)
	Asthma at 6 years	43/1256 (3.4)

Abbreviation: RAST, radioallergosorbent test.
[a] Tested at 12 months; positive result, immunoglobulin (Ig) E level of ≥0.35kU/L.
[b] Tested at 12 months; positive result, IgE level of 0.18-0.34 kU/L.
[c] Not including children with eczema within the first 12 months.

Descriptive Analyses

In the tests performed at 12 months of age, 10.9% of the patients were sensitized (≥0.35 kU/L) to at least 1 allergen and 2.7% to 2 or more allergens. Sensitization to food allergens (9.8%) was more common than sensitization to aeroallergens (2.3%). On testing for atopic disease at the age of 6 years, eczema was found in 10.6% of the children, allergic rhinitis in 8.1%, and asthma in 3.4% (Table 1).

Descriptive analysis showed early sensitization (at 12 months) to be associated with a higher prevalence of atopic disease at 6 years. This association was more pronounced for aeroallergens than for food allergens.

Milk and egg sensitization were both strongly associated with eczema at the age of 6 years; 22% of children with early egg allergen sensitization and 23% of those with early milk allergen sensitization had eczema at the age of 6. The prevalence of eczema in those without these sensitizations was around 10%. The strongest association between early sensitization and eczema at 6 years was found for cat allergen (43% of children). On excluding children with eczema within the first 12 months, however, the association between early sensitization and the subsequent development of eczema was no longer significant. Only children with eczema within the first year of life had aeroallergen sensitizations at the age of 12 months.

Similarly, aeroallergen sensitization was more relevant than food allergen sensitization for allergic rhinitis and asthma. Allergic rhinitis, for example, was present in 21% of children aged 6 years with early aeroallergen sensitization compared to 15% of those with early food sensitization and 7% of those without sensitization. The strongest association was seen for grass allergen; 38% of children with this sensitization had allergic rhinitis at the age of 6 years. Asthma, in contrast, was present in 14% of children aged 6 years with early aeroallergen sensitization compared to 11% of those with early food sensitization and 3% of those without sensitization. The strongest association was again seen for children with grass allergen sensitization (25%).

We also investigated the association between polysensitization (sensitization to ≥2 allergens) and atopic outcomes. The frequency of eczema at the age of 6 years increased with the number of sensitizations (9%, 18%, 29% for 0, 1, and ≥2 allergens, respectively). No such relationship, however, was found between polysensitization and either asthma or allergic rhinitis at the age of 6 years or eczema at 6 years only.

IgE Levels Between 0.18 and 0.34 kU/L

Just 17 children (1.6%) had low specific IgE antibody levels (between 0.18 and 0.34 kU/L) at 12 months. While the prevalence of eczema was higher in this group of children, the only statistically significant association was found between early food allergen sensitization and eczema at 6 years only (Table 2).

Multivariate Analyses

In multivariate analyses, early food and aeroallergen sensitization significantly increased the relative risk of all atopic outcomes; the highest ORs were found for the association between aeroallergen sensitization and asthma at 6 years (OR, 4.36; 95% CI, 1.38-13.78). For eczema, an association with aeroallergen sensitization was found only for children that already had eczema within the first 12 months (Table 3). Degree of polysensitization only increased the risk of eczema at the age of 6 years (sensitization to 1 allergen: OR, 1.98; 95% CI, 1.12-3.48; ≥2 allergens: OR 3.45; 95% CI, 1.52-7.81; data not shown).

Table 2. RAST Results for Children Aged 12 Months in Relation to Prevalence of Atopic Disease at 6 years

Positive RAST		Eczema at 6 Years			Eczema at 6 Years Only[b]			Allergic Rhinitis at 6 Years			Asthma at 6 Years		
		No.	%	*P* Value[a]	No.	%	*P* Value[a]	No.	%	*P* Value[a]	No.	%	*P* Value[a]
IgE≥0.35 kU/L													
Any allergen	0	105	9.4	.001	73	7.9	.948	81	7.3	.001	29	2.6	.001
	1	18	17.8		6	8.8		18	17.8		10	9.8	
	≥2	10	28.6		1	6.7		3	8.6		4	11.4	
Any food	No	107	9.6	.001	72	7.8	.221	82	7.3	.004	30	2.7	.001
	Yes	24	19.8		7	9.3		18	14.9		13	10.7	
Milk	No	120	10.1	.004	76	7.9	.172	97	8.2	.658	38	3.2	.049
	Yes	11	23.4		3	10.0		3	6.4		4	8.5	
Soy	No	129	10.5	.333	79	8.0	.509	98	8.0	.817	41	3.3	.247
	Yes	2	20.0		0	0		1	10.0		1	10.0	
Egg	No	107	9.4	.001	72	7.7	.683	81	7.1	.001	31	2.7	.001
	Yes	21	22.3		5	9.3		16	17.0		12	12.6	
Egg only	No	117	10.1	.065	73	7.8	.610	84	7.3	.001	34	2.9	.001
	Yes	11	17.5		4	10.0		13	20.6		8	12.5	
Any aeroallergen	No	125	10.2	.003	80	8.1	.286	96	7.9	.013	39	3.2	.002
	Yes	8	27.6		0	0		6	20.7		4	13.8	
Cat	No	125	10.2	.001	79	7.8	.556	97	7.9	.065	41	3.3	.026
	Yes	6	42.9		0	0		3	21.4		2	14.3	
House dust mite	No	131	10.6	.258	80	8.0	.434	100	8.1	.122	41	3.3	.002
	Yes	2	22.2		0	0		2	22.2		2	22.2	
Grass	No	129	10.7	.192	79	8.1	.674	96	7.9	.002	37	3.1	.001
	Yes	2	25.0		0	0		2	37.5		2	25.0	
IgE 0.18-0.34 kU/L													
Any allergen	No	97	9.3	.243	67	7.8	.083	74	7.1	.847	25	2.4	.519
	Yes	3	17.7		3	20.0		1	5.9		0	0	
Any food	No	102	9.5	.133	68	7.7	.041	79	7.4	.292	27	2.5	.548
	Yes	3	21.4		3	23.1		0	0		0	0	
Any aeroallergen	No	120	10.3	.241	76	8.0	.082	91	7.8	.71	34	2.9	.604
	Yes	2	22.2		2	25.0		1	11.1		0	0	

Abbreviation: RAST, radioallergosorbent test.
[a] Calculated using $\chi 2$ test.
[b] Excluding children with eczema within the first 12 months.

Table 3. Multivariate Logistic Regression Analysis for the Association Between Sensitization Versus No Sensitization at 12 Months and Atopic Outcome

	AOR[a]	(95% CI)
Eczema at 6 years		
Any allergen 0.5[b]	1.70	(0.36-8.04)
Any allergen[c]	2.31	(1.42-3.74)[d]
Food allergen[c]	2.15	(1.29-3.60)[d]
Aeroallergen[c]	3.27	(1.37-7.84)[d]
Eczema at 6 years only[e]		
Any allergen 0.5	2.40	(0.48-11.89)
Any allergen	0.81	(0.34-1.96)
Food allergen	0.89	(0.37-2.17)
Aeroallergen[f]		
Allergic rhinitis at 6 years		
Any allergen 0.5	0.91	(0.11-7.26)
Any allergen	2.22	(1.31-3.78)[d]
Food allergen	2.13	(1.21-3.74)[d]
Aeroallergen	2.76	(1.06-7.18)[d]
Asthma at 6 years		
Any allergen 0.5[f]		
Any allergen	3.93	(1.98-7.76)[d]
Food allergen	3.93	(1.95-7.91)[d]
Aeroallergen	4.36	(1.38-13.78)[d]

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval
[a] Adjusted for family history of atopy, parental education, siblings, sex, study region, and type of milk feeding during first 4 months of life.
[b] Immunoglobulin (Ig) E level of 0.18-0.34 kU/L versus no sensitization (IgE, <0.18 kU/L).
[c] IgE level of ≥0.35 kU/L versus no sensitization (IgE, <0.18kU/L).
[d] Significant ($P<.05$).
[e] Excluding children with eczema within the first 12 months.
[f] Not estimated due to scarcity of data.

Discussion

Sensitization is suspected to be a risk factor for the development of atopic diseases. In the present study, children sensitized to common food and aeroallergens at an early age had an increased risk of atopic disease at 6 years of age. Early aeroallergen sensitization was a particularly strong predictor for eczema, allergic rhinitis, and asthma later in life. Early sensitization in children without eczema in the first year of life, however, was not a risk factor for later eczema.

The GINI group used for this study is a large prospective birth cohort with a good response to questionnaires up to the sixth year of life. Early blood tests were also available for about 70% of the cohort, independently of atopic family history, gender, or later onset of atopic disease.

The sensitization rate of 10.9% detected in children aged 1 year is consistent with results published by the few other birth cohort studies (mostly population-based studies) that have conducted a blood test so early in life [10-13]. In our study, sensitization to food allergens was common in the first year of life (9.8%) while that to aeroallergens was low (2.3%). The much higher sensitization rates (of approximately 20%) reported by other studies for children aged 3 or 4 years are mainly attributable to the increase in sensitization to aeroallergens with age [14-16]. Similar results have been reported by the Multicenter Allergy Study (MAS) [17,18], where the sensitization to aeroallergens rose from 1.5% at 1 year to 26% at 6 years; sensitization to food, in contrast, remained at about 10%.

While the prevalence of eczema and allergic rhinitis at the age of 6 years in our study is comparable to that reported by the International Study of Asthma and Allergies in Childhood (ISAAC) [1], that of asthma is lower. One explanation for this divergence might be that common asthma symptoms such as wheezing were included in the definition of asthma in ISAAC. Also, German doctors seem to be reluctant to diagnose asthma. Some of the discrepancies between our findings and those of other studies regarding the prevalence of asthma and sensitization to aeroallergens, egg, and cat allergen as a risk factor may be due to different definitions of atopic diseases or sensitization or to differences in lifestyles, food habits, and environmental factors.

In the present study, children who became sensitized to food or aeroallergens in the first year of life had a markedly higher risk of developing atopic disease by the age of 6 years. Even though two-thirds of the children with early sensitizations did not develop an atopic disease, they had a 2-fold to 4-fold increased risk of doing so in comparison to children without sensitization. Sensitization to aeroallergens had the greatest effect on eczema, asthma, and allergic rhinitis. For eczema, this was only true in the case of children that already had eczema within the first 12 months.

In agreement with our results, other studies have described the importance of sensitization to hen's egg in the development of atopic disease. Zeiger et al [19], for example, found that a positive prick test to egg at the age of 12 months was a highly predictive marker for atopic eczema up to the age of 7 years. For asthma and allergic rhinitis, this relationship was less clear, however. In another study, 80% of children sensitized to hen's egg by the age of 9 months developed an atopic disease by the age of 4 years [20]. Neither of these studies excluded children with early eczema. In the MAS study [18], children sensitized to hen's egg at the age of 1 year developed atopic eczema significantly more frequently than those without this sensitization (39.7% vs 10.8% respectively). In another study, only 25% of children with eczema and food sensitization before 36 months failed to develop asthma or allergic rhinitis by the age of 7 years [21]. Sensitization to food allergens up to the second year of life has also been shown to be predictive for asthmatic disease up to school age, independently of sensitization to aeroallergens [22].

Sensitization to aeroallergens alone has not been reported to present a higher risk of atopic disease [18,22]. While we did not find egg sensitization in the first year of life to be a significantly higher risk factor for the development of atopic disease by the age of 6 years than sensitization to other allergens, we did find aeroallergen sensitization to be associated with a markedly higher risk. Hen's egg sensitization alone was not a significant risk factor for eczema at 6 years. In 1 study conducted on the Isle of Wight, 68.4% of children with sensitization to house dust mite at the age of 4 years had atopic disease and the risk

increased with the number of sensitizations detected [14]. In another study, the risk of atopic disease at the age of 4 years increased with the number of sensitizations to pollen [16]. In our study, polysensitization to 2 or more allergens increased the risk of eczema but not that of allergic rhinitis, asthma, or eczema at 6 years only.

While the German study LISA did not show an association between cat allergen exposure in infancy and allergic symptoms up to the age of 6 [23], there is clear evidence that cat sensitization is strongly associated with atopic disease, and asthma in particular, in children and adults [24,25]. However, to the best of our knowledge, our study is the first to have examined the risk of very early cat sensitization in the development of atopic disease later in life. Although only a few children in our cohort were sensitized to cat allergen, these children had the highest risk for developing atopic disease later in life. Perhaps this association has not been analyzed in depth to date because very few children are sensitized to aeroallergens, and cat allergen in particular, at such a young age. Indeed the much more frequent sensitization to egg allergen has been used as a marker of sensitization in general. A recent study in school-aged children also showed that cat-specific IgE was the strongest predictor for eczema, allergic rhinitis, and asthma in young adulthood [26].

We found that aeroallergen sensitization was the strongest predictor of later atopic disease, a finding that is consistent with reports by other studies. In 1 study of 4-year-old children with aeroallergen sensitization, 36% had atopic eczema, 39% had allergic rhinitis, and 17% had asthma [16], and in another, aeroallergen sensitization was much more strongly associated with atopic eczema than with asthma [7]. One possible explanation is that the definition of asthma is still inaccurate in children aged 6 years [27] as early wheezers frequently lose their symptoms and early childhood asthma is often triggered by infection and is hence independent of pre-existent sensitization. Nonetheless, Illi at al [28] showed that sensitization to perennial allergens in the first 3 years of life predicted asthmatic disease at school age, while wheezers without sensitization lost their symptoms later in life.

In our study, early sensitization was a risk factor for eczema at the age of 6 years only for children that already had eczema within the first 12 months. Most studies investigating the association between early sensitization and subsequent eczema have not excluded children with early eczema [19,20]. In 1 study that did exclude children with eczema in the first 6 months of life, sensitization to food allergens was still associated with an increased risk of developing eczema at school age [29] whereas in another study, which excluded children with eczema at 18 months of age, sensitization was no longer a risk factor [30]. As our first questionnaire was administered when the children were 1 year old, we do not know when exactly the eczema or early sensitization developed during the first year of life. The different results reported by the above studies and our study might be due to differences between onset of eczema before and after the age of 6 months. The 2 studies mentioned above [29,30] reported that eczema itself was a risk factor for later sensitization and that early sensitization was a risk factor for later atopic disease. One possible explanation for why eczema predisposes to sensitization is that the loss of integrity of skin as a barrier exposes antigen-presenting cells to environmental allergens [31]. Finally, long-lasting eczema in school children seems to be triggered more often by sensitizations than by infant eczema, which in many cases disappears by the time children have reached school age [32]. We found that children with very low sensitization levels (0.18-0.34 kU/L [RAST class, 0.5]) had an increased risk of developing eczema by the age of 6 years. The association, however, was statistically significant only for early food allergen sensitization and eczema at 6 years only, possibly due to the small number of children in the low sensitization group. Only 1 study has examined low-level IgE sensitization to house dust mite (0.23-0.35kU/L) in 6 month-old infants with wheezing and/or eczema [33]. All 15 infants with low-level IgE had developed IgE levels of over 0.35 kU/L by the age of 5. At this age, bronchial asthma and atopic dermatitis were significantly more common in children with house dust mite sensitization than in those without but the authors did not directly analyze whether early low-level sensitization was a risk factor for later atopic disease.

In a Danish study, high-level sensitizations (≥4.00 SU/mL) and polyvalent sensitizations were more strongly associated with atopic eczema at the age of 18 months than were lower IgE levels (≥1.43 SU/mL) [12], and Nickel et al [18] showed that IgE levels of over 2 kU/L had a higher positive predictive value for sensitization to aeroallergens at the age of 3 years than did lower IgE levels. They also found that these children had a higher prevalence of atopic dermatitis at the age of 12 months [18].

Some study groups that have used quantitative analysis of IgE antibodies to analyze the likelihood of allergic disease and predict symptomatic food allergy have found higher IgE levels to be significantly more prevalent in children with allergic disease and/or food allergy [34,35].

Conclusion

Sensitization to common food allergens, and aeroallergens in particular, during the first year of life was found to be a strong predictor for the development of atopic disease by the age of 6 years in children with a positive family history of atopy.

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