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Ninety hyperactive children, 22 children with learning disability and eight emotional-inattentive children were tested for allergy to 43 food extracts using the in vitro radioallergosorbent test (RAST). Fifty-two percent of all children exhibited allergy to one or more of the foods tested. Within the hyperactive group a statistically significant association was found between the number of allergies and teachers' (Conners) scores of hyperactivity. This association was statistically significant only in those hyperactive children who also had learning disability and minimal brain dysfunction. A statistically weak association was also found between a small number of children clinically diagnosable as hyperactive and the number of allergies or total allergy scores. A causal relationship between food allergy and a small subgroup of children with a primary diagnosis of hyperactivity is suspected.

FOOD ALLERGY IN CHILDREN WITH HYPERACTIVITY, LEARNING DISABILITIES AND/OR MINIMAL BRAIN DYSFUNCTION

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Introduction

Hyperactivity is usually present in 10-15% of the child population, being predominant in males.[1] The label of hyperactivity is commonly attached to children who are chronically inattentive, distractible and impulsive.

It is becoming increasingly apparent that hyperactivity is etiologically complex. Among the many factors that have been implicated as contributing to hyperactivity are included neurological complications following prenatal or perinatal trauma,[2] smoking during pregnancy,[3] hereditary and congenital factors,[4] environmental pollutants, particularly metals such as lead,[5] artificial additives in foods[6,7] and exposure to fluorescent lights.[8]

As a clinical syndrome hyperactivity is often confused by the uninitiated with learning disability and/or minimal brain dysfunction. However, careful studies of hyperactive children have revealed that while hyperactivity, learning disability and minimal brain dysfunction may co-exist, some hyperactive children do not have either learning disabilities or minimal brain dysfunction. Furthermore, not all children with minimal brain dysfunction or learning disability are hyperactive.[9]

This study is part of a larger investigation aimed at the development of a rationale for treatment of the hyperactive child. The main objective of this study was to investigate the presence, incidence and significance of food allergies in hyperactive children, including some with learning difficulties or minimal brain dysfunction.

An additional aim of this study was to assess in these children the existence of potential patterns of interrelationships among the number and severity of food allergies and hyperactivity, learning disability and/or minimal brain dysfunction. A clear understanding of the existence of such interrelationships is obviously important in developing a rationale for the treatment of hyperactivity.

Materials and Methods

Selection of Patients

Hyperactive, learning disabled and emotional-inattentive children were selected from a large pool of children referred to the Neuropsychology Laboratory of the Royal Ottawa Hospital for clinical evaluation. In addition to procuring extensive medical histories, complete school records and anamnestic data were obtained on each child. Each child received a 6-8 hour neuropsychological examination which consisted of IQ tests, academic achievement tests, specific tests of language and perceptual function and a standardized

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motor and sensory evaluation.[10]

The study included three groups: 90 hyperactive children; 22 children with learning disabilities and retardation in academic skills by at least one grade, but who were not hyperactive, and eight children with restlessness and inattentiveness in association with chronic anxiety states, also not hyperactive. A diagnosis of hyperactivity was based primarily on the neuropsychological (clinical) ratings for each child. In the final assessment of hyperactivity the pediatrician's diagnosis and Conners Parent and Teacher Rating Scales with a cut-off score of > 50% were also used.[11] The learning disability group were children of normal intelligence who were at least one grade behind class placement in reading, spelling or arithmetic levels but displayed no evidence of restlessness or distractibility characteristics of hyperactive children.

On the basis of the neuropsychological assessment, each child was further classified with respect to evidence of brain dysfunction. Each child in the hyperactive and emotional-inattentive groups was also examined for the presence of learning disabilities (Table I).

Allergens

The food extracts of cheese (American cheddar), salmon, white fish, shrimp, lobster, beef, lamb, chicken, pork, turkey, peas, peanuts, soybeans, almonds, walnuts, pecans, corn, barley, whole wheat, oats, rye, buckwheat, lentil, chocolate/cocoa, cucumber, banana, orange, tomato, cauliflower, garlic, onions, ginger, mint mix, tapioca, whole milk (bovine), casein (bovine milk) and whey (bovine milk) extracts (1:10 w/v in 50% glycerin) were purchased from Hollister-Stier Laboratories (Mississauga, Ontario, Canada). These extracts were dialyzed against double-distilled water (Cellulose dialysis tubing, 4.8 nm pore diameter, Fisher Scientific Co., Ltd.) for two days, lyophilized and stored at 4°C until needed. The powder forms of β-lactalbumin (bovine milk), bovine serum albumin, egg white (chicken), and egg yolk (chicken), were obtained from Sigma Chemical Company (St. Louis, Missouri, U.S.A.) and β-lactoglobulin (bovine milk) from ICN Pharmaceuticals, Inc. (Cleveland, Ohio). All antigen dilutions were made in phosphate buffered saline (PBS, 0.15M NaCl, KH_2HPO_4, and Na_2HPO_4 pH 7.2)

Allergy Questionnaires

Prior to blood collection, information pertaining to allergies in the child and his/her family (siblings, parents and grandparents) was obtained by directly interviewing the patient and his/her parents utilizing an itemized allergy questionnaire. The family of a child was considered positive for history of allergy if one of the parents or grandparents was clinically positive for one or more of the following symptoms: asthma, hay fever, eczema or hives.

Blood Samples

Blood was collected by venipuncture and allowed to clot overnight at 4°C. The serum was collected by centrifugation, sterilized by filtration through a double 0.45μ millipore filter (Millipore Ltd., Mississauga, Ontario), distributed in aliquots and frozen at -20°C until tested.

Coupling of Allergens to Activated Paper Disks

A hundred cellulose paper disks, (Whatman's filter paper, #54, hardened) each having 0.5 mm diameter and previously activated by reaction with cyanogen bromide,[12] were incubated with 10 ml of the antigen dilution (0.1-1.0mg/ml) for 18 hours at room temperature with constant rotation (Fisher roto-rack). After coupling, the discs were washed five times with 20 ml of cold PBS and the unreacted sites blocked with 0.1M ethanolamine, pH 9.0, containing 0.5% bovine serum albumin, for three hours at room temperature with constant rotation. Subsequently the disks were washed five times with PBS, blotted dry, lyophilized and stored at 4°C until used.

Assay of Reaginic (IgE) Antibodies

Phadebas Radioallergosorbent (RAST) kits (Pharmacia Laboratories, Montreal, Quebec) were used to determine serum IgE antibodies directed against specific food allergens.[13-15] Radioactivity in the test and control tubes was measured using a Gamma Counter (Beckman Gamma 300 System, Beckman Instruments Inc., 1117 California Avenue, Palo Alto, California, U.S.A.).

Scoring System

RAST scores (0-4) were based on a serially diluted reference serum supplied by Pharmacia. A score of one or greater (≥ 1) was considered as positive and the results were compared to those obtained when a RAST score of two and above (≥ 2) was taken as positive.

A *total allergy score* was calculated for each child by adding the scores for the individual allergens at a RAST score ≥ 1. For example, if child A was positive for soybean and corn RAST scores of four and two respectively, the *total allergy score* would be six. Similarly, the *number of allergies* was calculated for each subject by counting the number of foods to which a positive (RAST) reaction was obtained. In the above example the number of allergies for child A would be two.

Table I. Age, Sex and Learning Disability or Minimal Brain Dysfunction Status in 120 Children Divided into Groups.

	Subjects					
Group	Age in Years (Average)	Sex Ratio Male/ Female	Learning Disability Ratio	%	Minimal Brain Dysfunction Ratio	%
Hyperactive	8.59	77/13	64/90	71	39/90	43
Learning Disability	10.27	14/8	22/22	100	9/22	40
Emotional-Inattentive	10.25	7/1	5/8	63	4/8	50

Statistical Methods

Standard chi-square tests[16] were used (a) to compare the incidence of food allergy among the hyperactive, learning disability and emotional-inattentive groups, (b) to assess the association between food allergy and clinical evaluation of hyperactivity based on the total sample and (c) to compare the proportion of children whose parents had a positive allergy history among the three groups.

Table II. Analysis of RAST Results in 120 Children Using 43 Different Food Allergens.

Allergens	Positive Reaction ⩾ 1 (RAST score)		⩾ 2 (RAST score)	
	Number of Children	%	Number of Children	%
α-lactalbumin	2	2	1	1
β-lactoglobulin	2	2	2	2
Whey (bovine milk)	2	2	1	1
Egg white (chicken)	7	6	2	2
Egg yolk (chicken)	5	4	3	3
Salmon	3	3	1	1
Shrimp	5	4	1	1
Beef	32	27	17	14
Chicken	31	26	19	16
Pork	26	22	12	10
Turkey	8	7	2	2
Peanuts	2	2	2	2
Soybean	20	17	3	3
Almonds	6	5	3	3
Barley	11	9	6	5
Whole wheat	13	11	3	3
Oats	37	31	17	14
Rye	13	11	8	7
Lentil	2	2	1	1
Cauliflower	2	2	1	1
Garlic	6	7	1	1
Low positive*	1	1	1	1
Negative!	0	0	0	0

*RAST score of one: Whole milk (bovine), casein (bovine milk), cheese (American cheddar), white fish, lobster, lamb, walnuts, peas, pecan, corn, buckwheat, chocolate, cocoa, banana, orange.

! Cucumber, tomato, onions, ginger, mint mix, tapioca, bovine serum albumin.

Table III. Incidence of Food Allergy (RAST) in Children in the Hyperactive, Learning Disabilities and Emotional-Inattentive Groups.

Group of Children	Number of Children	Positive Reactions ⩾ 1 (RAST score) Ratio	%	⩾ 2 (RAST score) Ratio	%
Hyperactive	90	42/90	47	27/90	31
Learning Disabilities	22	17/22	77	7/22	32
Emotional-Inattentive	8	3/8	38	1/8	13

The technique of jackknifing the inverse hyperbolic tangent of the Pearson correlation coefficients[17] was used to test for independence of the number of allergies and total allergy score with parents' or teachers' ratings for hyperactivity alone, hyperactivity combined with inattentiveness, and the triad of hyperactivity, inattentiveness and conduct problems. Parents' ratings were not available for one child and teachers' ratings were unavailable for 13 children. One subject with 34 allergies was considered to be an outlier and was excluded from the analysis.

Results

At a RAST score of ⩾1, allergies were detected against most of the 43 food extracts tested (Table II). The number of allergies per child ranged from 0-34. The few extracts against which allergies were not found included those of cucumber, tomato, onion, ginger, mint, tapioca and bovine serum albumin.

Using the same RAST score of ⩾1, it was revealed that the incidence of allergy among the hyperactive, learning disability and emotional-inattentive groups of children varied significantly ($P<0.05$). Thus, a 77% incidence of allergy in the learning disability group was significantly higher ($P<0.05$) than the incidence of allergy in the hyperactive (47%) and emotional-inattentive (38%) groups (Table III). Also, the average number of allergies per group decreased from 1.84 in the hyperactive group to 1.77 in the learning disability group, to 0.88 in the emotional-inattentive group. Similarly, the average total allergy score decreased from 2.66 in the hyperactive group to 2.32 in the learning disability group to 1.00 in the emotional-inattentive group.

At a RAST score of ⩾2 the incidence of allergy in the hyperactive group was 31%, in the learning disability group 32% and in the emotional-inattentive group 13% (Table III). Statistical comparisons between these percentages proved that the differences in the incidence of allergy among these three groups were not significant ($P>0.05$).

A probe to assess the possible genetic influence on the high incidence of allergy observed in the learning disability group relative to the other two groups disclosed that 64% of the children in this group and 50% of those in the hyperactive or the emotional-inattentive groups had either parents and/or grandparents with a positive history of allergy. However, these differences among groups in the incidence of family allergy were not statistically significant ($P>0.05$).

The search for the existence of patterns of interrelationships between food allergy and the conditions of hyperactivity, learning disabilities or minimal brain dysfunction was carried out using a triple approach:

1. When the parents' or teachers' scores (Conners Questionnaires) for hyperactivity alone, hyperactivity combined with inattentiveness and the triad of

hyperactivity, inattentiveness and conduct problems were compared with the number of allergies or the total allergy score it was found that (a) there was a statistically significant ($P<0.05$) positive correlation between the teachers' scores for hyperactivity and the number of allergies (Table IV), (b) the teachers' scores for hyperactivity and inattentiveness also correlated significantly ($P<0.05$) with the number of allergies (Table IV), (c) parents' scores for hyperactivity did not correlate significantly ($P>0.05$) with the number of allergies or the total allergy score (Table IV), (d) there was a statistically significant ($P<0.05$) correlation between the teachers' scores for hyperactivity and inattentiveness and the total allergy score (Table V) and (e) after the group of hyperactive children was further subdivided into the subgroups of learning disability with minimal brain dysfunction, learning disability without minimal brain dysfunction, and without learning disability or minimal brain dysfunction, a statistically significant ($P<0.05$) positive correlation was found between the number of allergies and the teachers' scores for the subgroup of hyperactive children who also had learning disability and minimal brain dysfunction (Table V).

2. When the number of children with clinically diagnosable hyperactivity was compared with their respective number of allergies or total allergy score it was revealed that (a) there was a weak association between the presence of clinically diagnosable hyperactivity and the number of allergies ($P=0.051$) or total allergy score ($P=0.059$) (Table V), (b) The incidence of food allergy among children who were not clinically hyperactive was 67% while the incidence among those children who were clinically hyperactive was 45% (Table VI) and (c) the percentage of children clinically diagnosable as hyperactive and positive for food allergy increased proportionally with the number of allergies or the total allergy score (Figure 1).

3. When the 120 children in this study were classified into groups according to the presence of learning disability or minimal brain dysfunction (based on results

Table IV. Correlation of Number of Allergies or Total Allergy Score and Conners Rating Scores in the Hyperactive Group.

Conners Questionnaire	Number of Allergies		Total Allergy Score	
	No. of Subjects	Correlation Coefficient	No. of Subjects	Correlation Coefficient
Parents' rating for hyperactivity	88	-0.09	88	-0.10
Teachers' rating for hyperactivity	77	0.26 [a]	77	0.22
Teachers' rating for hyperactivity and inattentiveness	77	0.22 [a]	77	0.19
Teachers' rating for hyperactivity, inattentiveness and conduct problems	77	0.17	77	0.14

[a] Significantly different from 0 ($p < .05$) two-sided test.

Table V. Correlation of Number of Allergies or Total Allergy Score and Conners Rating Scores in Hyperactive Children with Learning Disabilities and Minimal Brain Dysfunction.

Conners Questionnaire	Number of Allergies		Total Allergy Score	
	No. of Subjects	Correlation Coefficient	No. of Subjects	Correlation Coefficient
Parents' rating for hyperactivity	37	.08	37	.05
Teachers' rating for hyperactivity	31	.40*	31	.35
Teachers' rating for hyperactivity + inattentive	31	.40*	31	.37*
Teachers' rating for hyperactivity + inattentive + conduct problems	31	.28*	31	.24

*Significantly different from 0 ($p < .05$) two-sided test.

Table VI. The Relationship (Chi-square) Between Clinically Evaluated Hyperactivity and Number of Allergies or Total Allergy Score.

Number of Allergies	Clinically Hyperactive			Total Allergy Score	Clinically Hyperactive		
	Yes	No	%		Yes	No	%
0	46	10	82	0	46	10	82
1	10	11	50	1	6	7	46
2-3	11	4	73	2-3	11	7	61
4-5	6	2	75	4-5	7	3	70
>6	10	3	78	>6	13	3	81

$X^2 = 9.42$ D.F. = 4 p = .051 $X^2 = 9.06$ D.F. = 4 p = .059

X^2 = chi-square

D.F. = degrees of freedom

p = probability

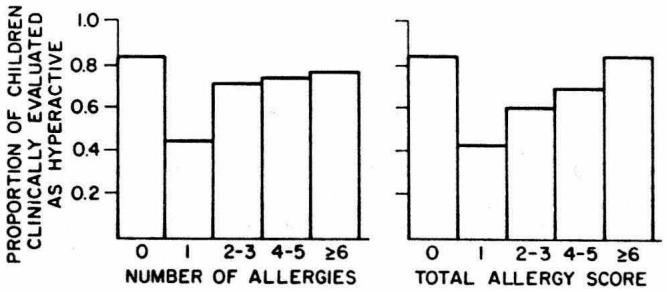

Figure 1. Percentage of children clinically evaluated as hyperactive in relation to number of allergies and total allergy score.

of the neuropsychological assessment and ignoring the presence of hyperactivity or emotional-inattentiveness) it was shown that the association between the number of allergies or total allergy score with the conditions of learning disability or minimal brain dysfunction was not statistically significant ($P>0.05$).

Discussion

The results of the RAST studies revealed a high incidence of food allergy in the hyperactive, the learning disability and the emotional-inattentive children. The incidence of food allergy (RAST score$\geqslant$1) in the learning disability group was much higher than in the hyperactive or emotional-inattentive groups. However, when compared with those of the learning disability and emotional-inattentive groups, the average number of allergies and average total allergy score were higher in the hyperactive group. In view of this observation and considering that at a RAST score of $\geqslant$2 the observed differences in the incidence of allergy among the three groups were not statistically significant, it was concluded that the high incidence of food allergy in the learning disability group was due to the presence, in this group, of several children with a single (RAST score one) allergy.

Analysis of the presence of allergy in the families of all 120 children included in this study revealed that the higher incidence of allergy in the learning disability group relative to the hyperactive and emotional-inattentive groups was not due to genetic factors but possibly due to differences inherent among the three groups. This conclusion was based on the finding that, although 50% of the families had a positive history of allergy, there were no significant differences in the incidence of allergy among the families of the hyperactive, learning disability and emotional-inattentive groups of children.

In addition to this finding the indication of the existence of a possible relationship between presence and extent of food allergy and clinically diagnosable hyperactivity is of potential importance in the treatment of hyperactivity. The results clearly indicated that a large number of hyperactive children did not have allergies to the foods tested. In view of the etiological complexity of the hyperactivity syndrome it was concluded that in these children hyperactivity may be due to factors other than food allergy.[2-6] It is possible that a proportion of these children are allergic to substances such as pollens, animal dandruff, molds, etc.[19-21] not tested for in the present study. Of interest, however, is the observation that the proportion (albeit small) of children positive for food allergies exhibiting clinically diagnosable hyperactivity increased as the number of food allergies and the total food allergy scores increased (Figure 1). This trend indicated that food allergies may have an additive effect. Thus, an individual may be only weakly sensitive to a number of foods but if he or she happens to consume all or a large number of such foods within a short period of time he or she may develop allergic symptoms and possibly hyperactivity.

A further indication that food allergy may be associated with hyperactivity is the existence of a statistically significant positive correlation between the teachers' ratings (Conners) of hyperactivity and the number of allergies detected (Table V). This association was significant only in those hyperactive children who also had learning disabilities and minimal brain dysfunction. The latter observation suggests that the effect of food allergy on hyperactivity would be more pronounced in children who suffer from learning disabilities and minimal brain dysfunction concurrently. In studies, currently underway, we are investigating in a double-blind, crossover design the effect on the children's behavioral problems of elimination from their diet of the foods against which a positive RAST result was obtained.

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HEALTH

"Each person ought neither to be unacquainted with the peculiarities of his own pulse (for there are many individual diversities), nor ignorant of any idiosyncrasy which his body has in regard to temperature and dryness, and what things in actual practice have proved to be beneficial or detrimental to it. For the man has no perception regarding himself, and is but a blind and deaf tenant in his own body, who gets his knowledge of these matters from another, and must inquire from his physician whether his health is better in summer or winter, whether he can more easily tolerate liquid or solid foods, and whether his pulse is naturally slow or fast. For it is useful and easy for us to know things of this sort, since we have daily experience and association with them."

Plutarch, *Moralia, "Advice About Keeping Well."*