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Clinical practice
Controlled trial of hyposensitisation in children with food-induced hyperkinetic syndrome

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Food intolerance seems to be an important cause of the hyperkinetic syndrome, but restricted diets are expensive, socially disruptive, and often nutritionally inadequate. Enzyme-potentiated desensitisation (EPD) may overcome some of these difficulties.

EPD was tested in a double-blind placebo-controlled trial among 40 children with food-induced hyperkinetic behaviour disorder. A total of 185 children with established hyperkinetic syndrome underwent oligoantigenic dietary treatment for four weeks. 116 whose behaviour responded had provoking foods identified by subsequential reintroduction. Foods that reproducibly provoked overactivity were avoided. 40 patients who were then invited to take part in the hyposensitisation trial were randomly assigned to treated and control groups. Treated patients received three doses of EPD (Beta glucuronidase and small quantities of food antigens) intradermally at two-monthly intervals. Controls received buffer only. Thereafter, patients were allowed to eat known provoking foods. Of 20 patients who received active treatment, 16 became tolerant towards provoking foods compared with 4 of 20 who received placebo ($p<0.001$).

Our results show that EPD result permits children with food-induced hyperkinetic syndrome to eat foods that had previously been identified as responsible for their symptoms. These results also support the notion that food allergy is a possible mechanism of the hyperkinetic syndrome.

Introduction

Food intolerance has been reported as a possible cause of the hyperkinetic syndrome. Avoidance of provoking foods in the treatment of choice for most patients who have this disorder. However, some patients react to foods that are difficult to avoid, and this creates difficulties in providing a nutritionally adequate diet. Others will not comply with the necessary dietary restrictions.

We have based both our dietary treatment and a pilot study of enzyme-potentiated desensitisation (EPD) on an allergy hypothesis. We now report a double-blind placebo, controlled trial of EPD in hyperkinetic children.

Patients and methods

Subjects

Subjects attended a special clinic to assess and treat overactive children by dietary means. The clinic was staffed by a paediatric neurologist (J.E.) and a dietician (A.S.). Children who were referred were diagnosed as having the hyperkinetic syndrome according to the

diagnostic criteria of DSM-III-R and ICD-9. The children had a more than one-year history of short attention span, distractibility, impulsivity, and poorly organised overactivity. In addition, children had to have a score of more than 15 on the short form of the Conners' scale. This scoring system was designed to assess behaviour at home. It consists of ten items of behaviour; overactive, excitable, impulsive; disturbs other children, fails to complete tasks, short attention span; constantly fidgeting; inattentive, easely distracted, demands must be most immediately, easily frustrated, cries often and easily, mood changes quickly and strikingly; temper outbursts explosive and unpredictable behaviour. Each is rated on a four-point scale: 0, not present; 1, mild; 2, moderate, 3, severe. A score of 14 or more indicates abnormal hyperkinetic behaviour. The severity of overactivity was graded according to care requirements: severe (unmanageable at home or at school); moderate (difficulty managing the child with a need for special help because of behaviour); and mild (manageable overactivity). Improvement was defined as a reduction in severity of grades. During the trial, no child received psychotropic medications. Other drugs (eg, antiobiotics) were given as colourless preparations. The study was conducted in four phases.

Phase I (oligoantigenic diet)

185 patients with the hyperkinetic syndrome received an oligoantigenic diet for 4 weeks. The diet consisted of two meats (eg, lamb and chicken), two carbohydrate sources (eg, potatoes and rice), two fruits (eg, banana and pears), vegetables (cabbage, sprours, cauliflower, broccoli, cucumber, celery, carrots), and water. Because of the nutritional inadequacy of the diet, it was supplemented with calcium, magnesium, zinc and vitamins. Patients who did not improve were offered a second oligoantigenic diet that consisted of foods not included in the first diet. 116 patients whose improvement was sufficient for their parents and teachers to think that dietary difficulties had been worthwhile and whose Conners' score fell below 15, entered the reintroduction phase. Those who did not respond were offered treatments with psychostimulant medication or behaviour modification.

Phase II (reintroduction of foods)

116 responders (Conner's scores <15) entered the reintroduction phase, during which provoking foods were identified by their subsequential reintroduction. Normal daily helpings of foods excluded from the oligoantigenic diet were reintroduced singly at the rate of one every five days. If hyperkinetic behaviour or other symptoms that had disappeared with the oligoantigenic diet were reproduced during at least three separate attempts to reintroduce a particular food, it was subsequently avoided. If not, it was incorporated into the diet. If essential foods provokes symptoms, others were substituted (eg, soya, gost or sheep milk for cow milk).

Phase III (double-blind, placebo-controlled trial of EPD)

Of patients with food-induced hyperkinetic syndrome, 54 with the most impressive change on diet were invited to take part in the randomised, double-blind, placebo-controlled trial; 40 accepted. They were randomised either to receive placebo or the active material three times intradermally at two-monthly intervals. Provoking foods were avoided during this period.

Each active intradermal injection consisted of Beta glucuronidase, mixed antigens, and food additives in a total volume of 0-2 buffer.

Molluscan Beta glucuronidase (Haliotis midos visceral humps; Seravac Ltd, Johannesburg) was prepared and formu-

lated with 1,3-cyclohexane diol and protamine as previously describe. Each active injection contained 200 Fishman units Beta glucuronidase, 50 pg 1,3-cyclohexane diol, and 50 ng protamine sulphate. Food antigens were extracted with Coca's solution. Samples of nut, cheese, meat and fish were comminuted, defatted with acetone as required, and extracted 10% dry weight/volume for one week at 4°C with frequent mixing. The material for extraction was not dried. Dry weight was determined by dessicating a sample and calculating the appropriate weight of wet material for extraction. After extraction, Buchner filtration was followed by membrane filtration steps. Final sterilisation was through a 0-22 gamma m pore size membrane filter (Schler & Schlercher, Dassel, Germany). Grain flours and yeat samples were subjected to the same extraction process. Whole raw egg was diluted to 10% in Coca's solution and filtered immediately. Cow milk (cream removed) and freshly expressed fruit juices were filtered directly and preserved with 0,5% phenol. (For subsequent standardisation purposes, milk was taken as 100% and fruit extracts as 10%). All extracts were stored until required at 4°C.

Foods extracts were mixed and passed through BioGel P6 column to remove preservative and substances of low molecular weight, and to transfer to the buffer solution used for treatment. During subsequent dilution and storage, the antigens were protected from adsorption by chondroitin-6-sulphate 0,2 mg/ml. The active injections contained 30 gamma m chondroitin-6-sulphate plus the extract of 2 fg dry weight of each food (or equivalent as explained above) except for foods with known crossreaction, which were obmitted or included at reduced doses. Mixed antigents included food extracts and additives. Food colours containing representative chemical groupings were selected for inclusion in the antigen mix. Food additives were present in the treatment at a dose calculated from the molecular weight to deliver 15.000 molecules of each.

The food antigens were: cow milk, cheddar cheese, brie cheese, stilton cheese, goat milk, goat cheese, egg, cod, herring, salmon, mackerel, aquid, prawn, crab, mussel, beef, pork, bacon, munton, chicken, white flour, brown flour, whole wheat, rice, maize, yeat, gartic, onion, potato, carrot, mushroom, spinach, banana, apple pip, grapefruit, hazelnut, brazilnut, almond, peanut, coconut, walnut, chocolate, green coffee. The colourings included were: tartrazine, chocolate brown, Poncesu 3R, erythrosin, green S, Annatto. The food preservatives were: butylated, methyl parahydroxybenzoate, benzoic acid, phenol. The placebo injection was buffer solution only.

Patients were randomised according to a table of random numbers. The only key was held by L.M. McEwen who supplied appropriate individual doses in consecutively numbered tubes delivered by courier. L.M. McEwen was not involved in the management and assessment of the patients.

Placebo and active treatment were both colourless solution. The intradermal injection of active formulation and placebo caused small areas of temporary erythems, which were indistinguishable. The site of each injection was immediately covered by a sticking plaster.

Phase IV (reintroduction of provoking foods)

Three weeks after the third injection, foods shown to provoke symptoms during phase II were again reintroduced one at time. Parents completed a daily diary card of hyperactivity and other symptoms. They were told that when food-related symptoms recurred and persisted for 24h they should stop the food. Results were analysed for stopping the first food given in the active and placebo group. When all foods had been reintroduced the parents were asked wheter the treatment had been succes-

sful in preventing or reducing symptoms on eating one or more of the provoking foods, these results were analysed. In general the foods were reintroduced in the order of nutritional importance.

Skin prick tests to five common antigens were done to identify atopic children (dermatophagoides, grass pollen, cat fur, milk and eggs). Serum IgE was also measured. The trial design was approved by the ethics committee of the University of Munich and informed consent was obtained from parents. Statistical analysis was by Fisher's exact test.

Results

The clinical features of the two randomised groups did not differ significantly, except that specific developmental delays and social isolation were significantly more frequent in the treated group. All but 4 had associated symptoms (eg, recurrent headaches, recurrent abdominal symptoms) in addition to overactivity. Prerequisites for entering the trial were recovery from the hyperkinetic syndrome and from other food-related symptoms on diet (Table I) and reproducible relapse when certain foods were eaten. The foods shown to cause reactions are listed in Table II.

The first food reintroduced to each child after the third intradermal injection of the coded material was stopped significantly more frequently in the placebo group than in the treatment group; of 40 patients, 1 was undecided and 3 left the study. 14 relapsed and the provoking food was discontinued, but 22 were able to continue to eat the previously identified provoking food with no major difficulties. Of these, 15 had been given EPD but only 7 placebo (Table III).

At the end of the study significantly more parents of children treated actively thought the treatment successful (Table III). These results depended on recurrence of any of the symptoms that had responded to diet (abdominal discomfort, bloaring, or diarrboes were usually first to appear). We observed no adverse effects from the treatment, except for the discomfort of the intradermal injection.

After the trial, patients who responded to active treatment continued to eat foods that no longer caused symptoms, until symptoms recurred after some months in all but 3. 13 patients who relapsed after 2-6 months were given single doses of EPD while back on the diet, which again seemed to relieve symptoms, but this was not tested directly by a placebo control. During 2-4 year's follow-up, the intervals between such relapses seem to have increased although they were shorter after viral infections. At the end of the trial to placebo group was also offered treat-

Table 1. Effect of dietary intervention

	Before diet	On diet
Hyperkinetic	40	0
Mean Conner's score	23	7-5
Headeaches	18	0
Abdominal symptoms	30	0

Table 2. Provoking foods before and after

	Active treatment		Placebo	
Food	Before	After	Before	After
Chocoless	11	3	17	15
Colourings	12	3	12	10
Cow milk	12	2	9	7
Egg	8	1	7	6
Cirrus	7	2	8	6
Weat	8	0	6	5
Beetsugar	8	2	6	5
Nuts	7	1	6	4
Cheese	5	1	6	4
Pork	3	1	3	2
	3	0	3	2
Banana	4	2	2	2
Tomato	2	1	3	1
Apple	2	0	2	2
Pears	2	0	2	2
	2	1	2	2
Beef	..	..	2	2
Fish	1	1	1	1
Apricots	..	..	2	2
	2	0	..	..

Table 3. Results of double-blind, placebo-controlled trial

	Analysis after reintroduction of first food			Analysis at end of trial (judgement by parents)		
–	Active treatment	Placebo	Total	Active treatment	Placebo	Total
Undecided	1	0	1	2	1	3
Left study	2	1	3	2	1	3
Unsuccessful	2	12	14	0	14	14
Successful	15	7	22	16	4	20
TOTAL	20	20	40	20	20	40

ment; after the third injection of EPD, 15 of 16 who accepted reported successful reintroduction of previously provoking foods.

The proportion of children (42,5%) who had positive skin-prick tests to one or more of the five antigens used to identify atopic children (dermatophagoides, grass pollen, catfur, milk and eggs) was similar to that in the general population. Of the 16 children who received active treatment and responded, 7 were atopi. The total IgE was raised in 19 patients; 8 received active treatment, 11 placebo. The parents of the 8 judged the treatment to be effective.

Discussion

The role of food intolerance in the hyperkinetic syndrome has been established by several trials. Various mechanisms have been suggested to account for such reactions to food. The design of the dietary treatment and the pattern of response suggest that an allergic mechanism is involved. Because of the difficulties of continuing dietary treatment, the notion of preventing the adverse response to provoking food is attractive and theoretically possible in allergic disease, but not in other forms of food intolerance.

Hyposensitisation for inhalant allergies has been substantiated by many trials, although the mechanism is unknown. The risks of hyposensitisation with large doses of antigen have led to the development of adjuvant-linked preparations that require lower doses; one of these is EPD. The application of such techniques to food allergic disease is limited, but our observation of apparent benefit for food-induced hyperkinetic syndrome to eat foods that had previously been identified as responsible for their symptoms.

No epidermiological studies have been done to establish the proportion of hyperkinetic children who react to foods. EPD is applicable only to those ptients whose hyperactivity responds to dietary treatment.

It is therefore important that children should not be given EPD unless food intolerance has been confirmed by established methods. Moreover, desensitisation should be reserved for patients with severe symptoms who can be shown to react to several different foods or to important foods.

In our study, EPD produced no serious adverse symptoms. At the time of each treatment, provoking foods were avoided and compliance was strictly supervised. The need to restrict the diet at the time of EPD was suggested in pilot studies by the appearance of urticaria and other symptoms some hours after injection in patient who did not adhere to the diet at the time of treatment. The doses of antigens given with EPD are in the range that will induce low-zone tolerance, and Beta glucuronidase seems to enhance this effect. Ingestion of normal amounts of food result in the absorption of substantial quantities of undigested food proteins, so eating offending food at the time of injection may interfere with the appropriate dose.

The mechanism by which EPD produces tolerance to provoking foods is not understood but, since the same method, but with inhalant antigens, is effective in the probably involved. Neverthless, unlike conventional desensitising injections that elicit blocking antibody titres, EPD with inhalent allergens does not induce blocking antibodies in successfully treated hay-fever patients (Dr M.S. Starr, personal communication). Moreover, antigen-induced leucocyte-migration inhibition is reversed after successful EPD desensitisation (Dr J. Brostoff, personal communication), suggesting a reduction in cellular responsiveness to antigen as opposed to some form of immunisation.

Sensitisation to new foods may take place in hyperkinetic children treated by diet, either at the time of viral infection or as the result of excessive intake of a previously "safe" food. It might be possible to prevent such new sensitisation by including all recognised provoking foods in the antigen mixture of the injected material. Thus, we judged it preferable to use the same comprehensive antigen mixture for all children in the actively treated group, although provoking foods were identified in phase II of our trial and hyposensitisation to only those foods would have been possible. Choice of food antigens, antigen mixes and the methods of extraction accorded with protocols that were established for immunotherapy for in the Wright Fleming Institute (London) 1908-79. Some foods present in the antigen mixture have common antigens. These were included at reduced dose. Others were omitted for the same reason. Previous work suggests that EPD is antigen-specific in animals (Starr et al, personal communication) and in man. By contrast, in this trial children who had previously reacted to sugar (not included in the antigen mixture) ceased to do so after active treatment. This observation was not significant and may have been a non-specific effect. Some components of the antigen mixes may not be needed to achieve hyposensitisation (eg, multiple varieties of cheese).

Restricted diets are socially disruptive, expensive, and, because of nutritional inadequacy, may be dangerous if not properly supervised. EPD offers the possibility of avoiding all of these difficulties.