A follow-up study of childhood food additive intolerance

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Intolerance to food additives was first documented by Lockey in 1959 when he reported that tartrazine could cause urticaria [1]. Subsequently, many groups, using placebo-controlled challenge studies [2-5], have recorded food additive intolerance with symptoms such as asthma and urticaria; the minority of studies involve children [6-8].

There have, however, been very few follow-up studies to indicate the duration of food additive intolerance in individual patients [8-11]. Some reports indicated that this was a transient phenomenon, but no large follow-up study has been made. This study was undertaken to investigate the duration of food additive intolerance in a group of children who had been studied as inpatients at one hospital and whose details have been reported [6].

Subjects and method

Thirty-four of 38 children previously studied were available for re-assessment. They were aged five to 18 years (mean 11.1, SD 3.71) and consisted of 21 boys and 13 girls. They had first been investigated between one and five years ago (mean 2.8 years). Their symptoms (see Table 1) had all shown improvement on an additive-free diet and their diagnosis had been established by double-blind, placebo-controlled, randomised single-substance food additive capsule challenges as inpatients (see Table 2). Five children reacted to three additives, 14 to two additives and 15 to one additive only (only one child reacted to the placebo, and was then excluded from further study). The additives to which they reacted are shown in Table 3. Six children also reacted to natural food challenges: milk 3, nuts 3, chocolate 1, wheat 1.

The children were contacted and the majority interviewed at least once (by J.P.). Those who had continued to avoid some additives and who considered they might still be intolerant of some food additives were re-challenged as outpatients. This was performed as a double-blind, placebo-controlled daily challenge with opaque capsules containing mixed additives supplied as 'low', 'high' and 'max' packs (Table 4). Glutamate and sulphite were never the only agents involved and were not re-tested. Symptoms were recorded by parents on a diary card at the end of the day, using a scoring system of 0 to 3. Capsules were only taken when there was no intercurrent illness or fever. At the end of the challenges, diary cards were returned and analysed blind before the code was broken.

Additionally, 20 children previously studied and found to be tolerant of the food additives were recontacted and re-assessed.

Results

Twenty of the 34 children did not react on rechallenge studies, while six children had returned to a normal diet when re-assessed. Five children are still undergoing challenge studies, and the parents of one child who still avoids some additives declined rechallenge studies. Thus, at least 26 out of 34 (76 per cent) children have been shown to have a transient additive intolerance (see Table 5).

It is interesting to note that one of the children on a normal diet has become an insulin-dependent diabetic but does not need to avoid additives.

Of the two children still intolerant to food additives, one is an eight-year-old male, who two years previously was shown to have an urticarial reaction to tartrazine, sodium metabisulphite and sodium benzoate; on rechallenge he re-developed mild cough and wheeze but no urticaria in response to aspirin and benzoate. The other patient was a six-year-old girl previously studied three years ago and found to have urticaria in response to sunset yellow, indigo carmine and monosodium glutamate (MSG) (see Table 6). On rechallenge, she developed mild itching in response to non-azo dyes. All the children were challenged with 'low' and 'high' dose packs, and five also proceeded to the 'max' challenge doses (see Table 4).

Only 15 of the 20 children originally found not to react to additive challenge could be traced. Ten (75%) had continued with a normal diet but five (25 per cent) did not agree with the original negative findings and continued to eliminate some additives from the diet (see Table 7).

Discussion

These results indicate that additive intolerance in this group of children is mainly a transient phenomenon.
Only two children could still be shown to react (one with subjective symptoms only) and even these required higher doses of additives than in the initial study. However, the majority of these children are now on a normal diet, having relaxed the dietary restriction, either spontaneously or on medical advice following the negative challenges. It is difficult to comment on the one child who still avoids additives and refused rechallenge.

In some respects the challenge methods differed from that of the initial diagnosis, albeit in a manner which would be expected to increase the likelihood of the child reacting. The outpatient rechallenges were repeated on at least two occasions with each substance ('low' and then 'high' dose) and they were performed with higher doses than in the initial studies (by a factor of 5-50).

Gibson and Clancy [9] rechallenged 12 patients with urticaria who had improved after one year on an additive-free diet, of whom 11 had reacted previously to challenges. Three out of four reacted again to sodium benzoate (500 mg), none of three reacted to tartrazine (10 mg) and five out of seven responded to aspirin. Thus tartrazine intolerance proved more transient than benzoate and aspirin intolerance. One patient, initially reacting only to benzoate, reacted to benzoate and aspirin on rechallenge. Ros et al. [10] followed up 75 patients with ‘recurrent’ urticaria 6-24 months after reacting to challenges with aspirin (1-1000 mg), azo dyes (1-10 mg) and/or benzoates (50-500 mg). Forty-eight had continued to eliminate substances to which they had reacted, of whom some reported relapses on relaxing their diet. No rechallenge studies were performed.

Warin and Smith [11] rechallenged 12 patients whose urticaria had been previously provoked by tartrazine (10 mg) and concluded that reactions occurred only when the urticaria was active, or shortly afterwards (3-8 weeks). Kauppinnen et al [8] followed up 132 children with urticaria of whom 13 per cent initially reacted to additive/aspirin challenges. After a mean time of 3.8 years, half of those who had initially reacted became symptom free, although whether or not they were on a normal diet is not clear.

These reports are in general agreement with our findings that food additive intolerance is a transient phenomenon in at least 26 out of 34 subjects. Two of the remaining eight children developed symptoms on rechallenge, the parents of one child declined rechallenge and five children are currently being reassessed. To obtain these results, this study is unique in systematically rechallenging a population of children with well-documented additive intolerance.

Of the 20 children who had a negative response to food additive challenges in the initial study (of whom 15 could be traced), 50 per cent continued asymptomatic on a normal diet (Table 7). However, the parents of five children did

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**Table 1. Additive-induced symptoms in 34 children.**

| Symptom               | No. of Patients |
|-----------------------|-----------------|
| Urticaria/angio-oedema| 26              |
| Gastrointestinal upset| 4              |
| Arthralgia            | 1              |
| Behavioural problems  | 1              |
| Rhinitis              | 1              |
| Asthma                | 1              |

**Table 2. Initial challenge doses of food additives.**

| Challenge compounds         | Challenge doses (mg) |
|-----------------------------|----------------------|
| Lactose placebo             | —                    |
| Tartrazine (E102)           | 0.1,0.5,1.0          |
| Sunset yellow (E110)        | 0.1                  |
| Amaranth (E123)             | 0.1                  |
| Indigo carmine (E132)       | 0.1                  |
| Carmoisine (E122)           | 0.1                  |
| Sodium benzoate (E211)      | 100                  |
| Monosodium glutamate (E621)| 100                  |
| Sodium metabisulphite (E223)| 10                   |
| Aspirin                     | 100                  |

**Table 3. Additive sensitivities in 34 patients.**

| Additive         | No. of patients |
|------------------|-----------------|
| Tartrazine*      | 18 (14)         |
| Indigo carmine   | 5 (4)           |
| Amaranth*        | 6 (4)           |
| Sunset yellow*   | 9 (5)           |
| Carmoisine*      | 1 (0)           |
| Sodium benzoate  | 7 (6)           |
| Monosodium glutamate | 5 (5)     |
| Aspirin          | 5 (5)           |
| Sodium metabisulphite | 4 (4)  |

*Figures in parentheses indicate reactions to other additives

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**Table 4. Additive dose in re-challenge packs.**

| Substance         | 'Low' | 'High' | 'Max' |
|-------------------|-------|--------|-------|
| Amaranth          | 0.5   | 2.5    | 25    |
| Sunset yellow     | 0.5   | 2.5    | 25    |
| Carmoisine        | 0.5   | 2.5    | 25    |
| Tartrazine        | 0.5   | 2.5    | 50    |
| Green S           | 0.5   | 1.0    | 10    |
| Quinoline yellow  | 1.0   | 2.5    | 10    |
| Indigo carmine    | 1.0   | 2.5    | 25    |
| Annatto           | 1.0   | 10.0   |       |
| BHA               | 1.0   | 50     |       |
| BHT               | 1.0   | 50     |       |
| Sodium benzoate   | 10    | 100    | 275   |
| Aspirin           | 50    | 300    |       |

**Table 5. Results of oral challenges.**

| Response                        | No. of Patients |
|---------------------------------|-----------------|
| Negative on rechallenge         | 20              |
| Undergoing challenge            | 5               |
| Normal diet (1 diabetic)        | 6               |
| On additive-free diet; declined study | 1          |
| Reacted on challenge            | 2               |

**Total** 34
not accept the negative findings of the challenge tests and continued to avoid additives. It is possible that they might have reacted, if tested initially to higher doses of additives, such as those used in the rechallenge study.

Our results suggest that there are two populations of children who are food-additive intolerant, the majority with transient intolerance, and a minority whose intolerance is persistent. These findings parallel the natural history of some food allergies, such as egg allergy, which has also been shown to be either transient or persistent [12]. This variation in duration of food additive intolerance may reflect different pathological mechanisms, but this remains speculative at present.

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