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Recovery from FPIES caused by fish. (Title)

Recovery from food protein-induced enterocolitis syndrome caused by fish.

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To the editor:

Adverse reactions to food in childhood are very frequent. Often they involve the skin, airways and gastrointestinal tract, and in severe cases circulation can also be affected, with a drop in blood pressure. These reactions can be either immunoglobulin E (IgE) -dependent or not. In IgE-dependent reactions, IgE antibodies to the food are detected in blood tests or skin prick tests. The pathomechanism behind non-IgE involvement reactions is, however, still not known. A defined type of non-IgE reaction to food is food protein-induced enterocolitis syndrome (FPIES). This entity was first evaluated in 1967 when Gryboski identified several children with chronic gastrointestinal allergy to milk which manifested as diarrhoea, vomiting and colic. The symptoms disappeared when proteins causing the symptoms were eliminated from the diet, and recurred when they were reintroduced (1).

Typical symptoms of FPIES usually occur 30 minutes to 4 hours after ingestion of the offending food protein. The most commonly responsible trigger foods are milk and soy proteins, but a variety of different proteins found in solid foods (e.g. rice, oats, barley, meat, fish, vegetables, fruits) can also cause this reaction (2). The symptoms of FPIES include vomiting, diarrhoea, bloody diarrhoea, lethargy and pallor, and even hypovolemic shock. Skin symptoms such as urticaria and pruritus as well as airways symptoms are absent (3).

Clinical history is the basis for diagnosis of FPIES but in cases where there is doubt about the diagnosis, food provocation can be considered. Furthermore, absence of increased levels of specific IgE antibodies to food strengthens the diagnosis (4).

The natural history of FPIES provoked by milk and soy is extensively studied and results show a good recovery rate. In a recent study, 90% of the included children tolerated milk by age of 3 (5). Development of natural tolerance for solid foods is, however, limited. The incidence of FPIES caused by fish seems to differ between countries. In the USA and Australia, reactions to fish are very seldom seen but in a report from Italy, FPIES reaction to fish is the most common reaction to solid food (4). The natural

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history of FPIES in children following ingestion of fish is sparsely studied and only a few reports have been published (4,6,7). In this study, we evaluate the development of tolerance in children with FPIES caused by fish protein.

Patients and methods

At our allergy clinic we identified patients with a history of unexplained vomiting, at least in two occasions after eating fish. Ten children, two boys and eight girls, born between 1996 and 2002 were identified. All children fulfilled criteria for FPIES (8) as they had reactions after eating codfish but they had no skin or respiratory symptoms. Vomiting started between 30 minutes and 4 hours after fish intake. Skin prick tests and/or blood tests for specific IgE for codfish were negative in all patients. Atopy patch testing (APT) was not performed. Nine children were between 9 and 30 months old when they had their first reaction after eating fish, with a mean age of 18 months. One child had been born moderately preterm and introduction to fish was delayed until 4 years of age for unknown reasons. The severity of reaction ranged from vomiting only (n=8) to vomiting with diarrhoea (n=1) and severe symptoms in need of intravenous treatment with fluids (n=1). Data is missing concerning other symptoms such as lethargy and pallor. Besides the reaction to fish, three of our patients had vomiting after consuming chicken and one of these also after eating egg. Four children had a history of classic FPIES and further diagnostic evaluation was not performed. In six children with vague history an oral provocation with codfish was undertaken. Five reacted with symptoms in the same way as before. In one of these children, provocation was delayed to 4 years of age and at that time no reactions were observed. This child had eliminated fish from their diet for 2 years. One of the children reacted with vomiting at age 4 but a new provocation 1 year later was negative. We decided to follow the children by administering a questionnaire to them at 11–17 years of age, in order to describe the recovery from FPIES caused by fish and also to record development of symptoms of IgE-mediated allergy. This study has not been evaluated by the ethics committee as it was performed as part of our clinical work.

Results

We received completed questionnaires for eight children. Five had developed tolerance to fish at between 4 and 8 years of age. These children had been either accidentally or deliberately provoked by fish outside the hospital. Three out of the eight children had at the time of answering the questionnaire still not been exposed to fish. Two of these, at the age of 11 and 12 years, respectively, underwent oral provocation with 20 ml codfish at the hospital and did not show any symptoms. One of those two patients was the child that had initially developed severe symptoms. In other words, they had developed tolerance and it is possible that this had developed much earlier. One child refused to take part in provocation.

Out of the eight, seven children have to date not developed allergy to either pollen or furry animals. Only one child from the group has developed pollen allergy. Notably two children have developed type 1 diabetes. Data are missing for the two non-respondents.

Discussion

Food protein-induced enterocolitis syndrome is an uncommon, non-IgE-mediated reaction to several food proteins and is manifested by repeated vomiting, often followed by diarrhoea, pallor and lethargy and sometimes even hypovolemic shock. Despite occasional severity of symptoms, no deaths have been reported in the literature. The low degree of awareness may be related to an underestimated prevalence of FPIES in society (9). However, during the last years there has been an increasing

interest in this syndrome, with several recent publications and studies, especially regarding reactions to cow's milk and soy. Several reactions due to solid foods have been reported, but fish seems to be an infrequent cause of FPIES. It is therefore remarkable that we have identified so many patients with this reaction.

All included children met the criteria for classic FPIES (8) while two out of ten children did not participate in this follow-up study and a third declined when invited to the clinic for food provocation. We have not done any evaluation for drop-out. Food protein-induced enterocolitis syndrome is a cell-mediated reaction and is in this study not linked to atopy.

In other studies a development from FPIES to IgE-mediated food allergy is commonly described. Still, FPIES is a new area in paediatrics that often leads to delayed diagnosis (9) Since the awareness is increasing and more patients are being identified, it is, however, hoped that we will learn more about this syndrome in the coming years.

We can conclude that FPIES caused by fish has a favourable outcome. Half of our ten patients had developed tolerance to fish by 4–8 years old, while two of the patients developed tolerance at 11 and 12 years of age, respectively. One patient refused provocation and data for the other two patients are missing. Regarding those provoked at 11 and 12 years, we assume that they had developed tolerance earlier. To precisely specify the age at which tolerance occurs, provocations should be done at regular intervals, but this was not done in this study. In our study, we did not find an increased risk for development of IgE-mediated allergy in children with FPIES provoked by fish.

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