CF: Allergenic Foods and Gluten

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The period of complementary feeding (CF) represents a significant part of the 1000-day critical window. In 1994, the minimum body weight of 5 kg was selected as the main criteria to wean preterm infants on solid foods by the “Committee on Medical Aspects of Food and Nutrition”. Later, the period between 5 and 8 months of uncorrected age was suggested for the initiation of CF in preterm infants. Corrected age (CA) is defined by American Academy of Pediatrics (AAP) as chronological age reduced by the number of weeks born before 40 weeks of gestation. Developmental signs of readiness include infants holding their heads up when sitting, showing interest in what others are eating and opening their mouths when food approaches. The introduction of allergenic foods and gluten has always been considered a challenge of CF in healthy full-term infants. In preterm infants, this is an issue of great concern.

Keywords: complementary feeding ; weaning ; preterm infants ; allergenic foods ; gluten ; celiac disease ; food allergy

1. Allergenic Food Introduction

Preterm infants were considered to be at higher risk of developing food allergies due to increased gut permeability [1], increased exposure to foreign food proteins and early introduction of solid foods [2][3].

Low levels of antibodies to cow’s milk and gliadin were found in preterm infants [4][5]. A large epidemiological study found a lower incidence of eczema in preterm infants compared to full-term infants [6]. Others have either confirmed the same results [7][8][9][10] or found no difference [11][12][13][14]. Only fetal growth restriction could be associated with increased risk of atopic disease [15]; however, Liem et al. [16] reported no significantly increased risks for food allergy development for either prematurity or low birth weight in the 1995 Manitoba Birth Cohort in Canada. Kvenshagen et al. [14] found no difference in the prevalence of IgE-mediated food allergies in children with atopic dermatitis between infants born preterm and full-term. Gut permeability appears indeed to rapidly adapt after birth, regardless of gestational age or birth weight [17].

Some studies proposed that preterm infants are at increased risk of allergies [2][3], notably those with a strong family history of atopy, with no direct link to breastfeeding or the time of allergenic foods introduction [18]. Increased risk of wheezing is mostly due to lung damage in the neonatal period [19]. In 2004, the observational study conducted by Morgan et al. [20] revealed that preterm infants who had four or more solid foods introduced before 17 weeks CA, or who had any solid foods introduced before 10 weeks CA, had an increased risk of eczema development. Furthermore, it suggested that introducing solid food starting from 3 months CA also reduced the potentially increased risk of eczema development. In contrast to this finding, another paper by the same group [21] demonstrated no association between the age of introduction of CF (≤12 or >12 weeks, post-term age) and the incidence of eczema (21% of the preterm infants developed eczema by 9 months CA). Yrjänä et al. [22] studied the timing of CF introduction in a cohort of 664 preterm infants: Late preterm infants started CF at a median CA of 1.9 months, without having an increased incidence of food allergies or atopic dermatitis. These data support the theory that the gut-associated lymphoid tissue of preterm infants is ready to meet food proteins and to begin the maturation process within 3 to 6 months, regardless of gestational age.

The most common pediatric food allergies are reactions to cow’s milk, hen’s egg, soy, peanuts, tree nuts, wheat, fish and shellfish. Although the majority of children with milk or egg allergies will become tolerant, few are at risk of developing atopic disorders or respiratory allergic diseases [23]. Over the last few years, there has been increasing evidence to support the early introduction of potentially allergenic foods to enhance the development of oral tolerance [24]. Furthermore, low incidence rates of peanut allergies can be observed in countries in which the culinary culture is rich in peanuts, and they are commonly used in the weaning process [25]. These studies are extremely valuable, as there is a significant rise in food allergies in high-income countries, where the current recommendation is to restrict and delay exposure to such foods. The development of immuno-tolerance to an antigen might require both repeated exposure, possibly during an early critical window, and modulation of other dietary factors including breastfeeding [26].

As a result, the European Society of Pediatric Allergy and Clinical Immunology (EAACI) and the ESPGHAN have produced joint guidelines [27].

In 2014 the EAACI Guidelines were released, providing evidence-based recommendations for primary prevention of food allergies [28]. The AAP's advice is to not limit the maternal diet throughout pregnancy and lactation [27]. All infants should be exclusively breastfed for the first 4–6 months of life [29][30][31][32]. Should this not be possible or should it not be in adequate measure, a hypoallergenic formula can be recommended to high-risk infants for the first 4 months [33], after which a standard cow's milk-based formula is recommended. After 4 months of age, CF is recommended, also for infants with a hereditary predisposition to atopy. No special measures should be taken in high-risk infants, neither withholding nor exposing them to "highly allergenic" foods, during the weaning process [34][28].

In 2016, a systematic review and meta-analysis by Ierodiakonou [35] showed that timing of introduction of allergenic foods was associated with the risk of allergic disease. Introducing eggs at 4–6 months of age was associated with reduced rates of egg allergy across the allergy-risk spectrum, from normal risk to very high risk, in the infant population. Prior sensitization may cause severe allergic reactions in case of exposure to raw pasteurized eggs instead of cooked or heated eggs [26]. The same paper [35] also conducted observations regarding peanut allergies, and the conclusions overlap with those regarding egg introduction: The exposure to peanuts between 4 and 11 months of age is associated with fewer peanut allergies. This is the same conclusion the normal-risk population-based trial EAT [36] and the high-risk population-based trial LEAP [37] reached. The LEAP study defines high-risk infants for peanut allergies as those with severe eczema, egg allergy, or both. Hence, this population should undergo early peanut exposure, following evaluation by an appropriately trained specialist, as recommended by 10 international pediatric allergy associations [38]. Furthermore, it was observed that the prevalence of peanut allergy was not increased in the follow-up of children from the LEAP trial [39]. The meta-analysis by Ierodiakonou concluded that early fish introduction was associated with reduced allergic sensitization [35].

These data conflict with previous recommendations to delay the introduction of allergenic foods to the infant's diet and suggests that current guidelines may need to be revised [28][40][41]. The EAT trial has proven that in normal-risk infant populations, the exposure to six different allergenic foods at a very early age, such as 3–4 months, was safe, with no evidence of adverse effects on breastfeeding [42]. The association between early allergenic food introduction and food allergy to the same food was limited to few studies, and it was only statistically significant for eggs and peanuts. The phenomenon of oral tolerance in humans has been demonstrated only recently [37][39]. Oral tolerance appears to be antigen-specific: Early introduction of one allergenic food does not influence the development of an allergy to a different allergenic food [35]. The findings may not be generalizable beyond food allergies mediated by IgE antibodies.

A systematic review of 14 studies by Larson [43] has put forward evidence stating that the delayed introduction, delayed being after 9 months of age, of potentially allergenic foods is associated with an increased risk of developing food allergies. Moreover, diets rich in fruits, vegetables and homemade foods seem to be associated with fewer food allergies [44].

2. Gluten Introduction

Celiac disease (CD) is a chronic, multi-organ autoimmune disease that affects the small bowel in genetically predisposed persons precipitated by the ingestion of gluten. Based on analysis of the Norwegian MoBa cohort, the development of CD in children is not associated with intrauterine growth [45].

Prevention of the occurrence of CD with infant feeding practices has been extensively discussed. In 2008, the ESPGHAN CoN recommended avoiding both early (<4 months of age) and late (>7 months of age) gluten introduction. It also recommended introducing gluten while breastfeeding [46]. A recent meta-analysis showed that the introduction of gluten after 6 months increased the risk of developing CD [47].

Two recent RCTs [48][49] and the TEDDY study [50] examined the effect of the age of gluten introduction on the risk of developing CD autoimmunity (CDA) or CD in children at genetic risk for CD. While the incidence of early (<2 years old) CD and CDA was improved, the overall prevalence during childhood was not reduced. Therefore, changing the timing of the introduction of gluten cannot be considered a primary prevention measure. Furthermore, the lack of trustworthy data regarding the safety of very early (<3 months old) gluten introduction has discouraged such behavior [51].

Breastfeeding had no preventive effect on the development of CDA or CD during childhood according to the systematic review by Szajewska [51]. Only limited case-control evidence suggests that breastfeeding for short durations or not at all is associated with a higher risk of a diagnosis of IBD and celiac disease, respectively [52].

Despite the negative results of studies testing different strategies of the timing of gluten introduction, a high quantity of gluten remains a suggested risk factor [53]. Higher gluten intake during the first 5 years of life was related to the increased risk of CDA and CD in genetically predisposed children among participants in TEDDY [54]. However, this result was not confirmed by a re-evaluation of another large study of similarly at-risk children who developed CD [55]. Recognizing the absence of effective prevention strategies, the ESPGHAN published modified guidelines regarding gluten introduction [56][57][58].

Even though breastfeeding should be encouraged for its well-known health benefits, neither any breastfeeding nor breastfeeding during gluten introduction has been demonstrated to influence the risk of CD [56][59]. Introducing gluten while the infant is breastfed cannot be recommended to reduce the risk of developing CD [56]. The type of formula (cow's milk protein or extensively hydrolyzed formulas) used to feed infants before 8 months of age did not affect the risk of developing CD [60].

Gluten may be introduced into the infant's diet anytime between 4 and 12 months of age. The age of gluten introduction in infants in this age range does not seem to influence the absolute risk of developing CDA or CD during childhood [56]. There is still much to define regarding the introduction of gluten during CF. No advice can be given as to which types of gluten should be used during CF.

ESPGHAN currently recommends avoiding large doses of gluten soon after its introduction and during infancy [26], despite limited evidence to support this recommendation. In the EAT Study [36], differently from other trials, gluten was introduced from age 4 months and in larger quantities: the findings from a prespecified analysis of the EAT trial indicate that early consumption of high-dose gluten should be considered as a strategy to prevent CD in future research [61].

No recommendation was made on gluten introduction in children from families with first-degree relatives with CD [56]. The very early development of CDA and CD (<3–5 years of age) seems to affect mainly children carrying the very-high-risk CD alleles (HLA-DQ2.5 homozygous), which are found in 1% to 2% of the general population but in 10% to 15% of children with first-degree relatives having CD. Earlier introduction of gluten (4–6 months) is associated with earlier development of CDA and CD in at-risk infants, although the cumulative incidence of both in later childhood is similar [62][46]. However, delaying the introduction of gluten may delay the onset of the disease, with potential benefit secondary to the maintenance of a state of health during a crucial period of child development [48].

It is well known that in children with no genetic predisposition for CD, the timing and mode of gluten introduction do not influence the risk. Though the recommendations are only valuable to genetically predisposed infants because they are the only ones at risk of developing CD after gluten introduction, the protocol must be applied to all infants, given that genetic risk alleles are generally not known at the time of introduction of CF [26][56]. Advice for preterm infants is extremely inadequate.

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