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Practice guidelines

Nutritional management of cow's milk allergy in children: An update

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ABSTRACT

Cow's milk is one of the most common foods responsible for allergic reactions in children. Cow's milk allergy (CMA) involves immunoglobulin E (IgE)- and non-IgE-mediated reactions, the latter being both variable and nonspecific. Guidelines thus emphasize the need for physicians to recognize the specific syndromes of CMA and to respect strict diagnostic modalities. Whatever the clinical pattern of CMA, the mainstay of treatment is the elimination from the diet of cow's milk proteins. The challenge is that both the disease and the elimination diet may result in insufficient height and weight gain and bone mineralization. If, during CMA, the mother is not able or willing to breastfeed, the child must be fed a formula adapted to CMA dietary management, during infancy and later, if the disease persists. This type of formula must be adequate in terms of allergic efficacy and nutritional safety. In older children, when CMA persists, the use of cow's milk baked or heated at a sufficient temperature, frequently tolerated by children with CMA, may help alleviate the stringency of the elimination diet. Guidance on the implementation of the elimination diet by qualified healthcare professionals is always necessary. This guidance should also include advice to ensure adequate bone growth, especially relating to calcium intake. Specific attention should be given to children presenting with several risk factors for weak bone mineral density, i.e., multiple food allergies, vitamin D deficiency, poor sun exposure, steroid use, or severe eczema. When CMA is outgrown, a prolonged elimination diet may negatively impact the quality of the diet over the long term.

1. Introduction

Breastfeeding is the optimal way of infant feeding, exclusively until 6 months of age and partially until 2 years according to the World Health Organization (WHO) [1]. Non-breastfed infants must be fed with infant formulas complying with the European regulations (Commission Directive 2006/141/EC on infant formulae and follow-on formulae, which will be replaced by the Delegated Regulation No. 2016/127), containing proteins generally obtained from cow's milk. Cow's milk allergy (CMA) is the most commonly reported childhood food allergy, even though community-based incidence and prevalence estimates vary widely, due to possible misinterpretations of presumed reactions to cow's milk and to differences in diagnostic criteria [2]. In children up to age 2 years of age from the EuroPrevall birth cohort (nine European countries), 0.54% had confirmed CMA, proven by Double-Blind Placebo-Controlled Food Challenge (DBPCFC) to milk, with variations from 1% in the Netherlands and the United Kingdom (UK) to less than 0.3% in Lithuania, Germany, and Greece [3]. CMA has multiple clinical manifestations; its management requires

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elimination of cow's milk protein (CMP)-containing products. This elimination diet may, among other factors, have a negative impact on the nutritional status of affected children. The purpose of this paper is to describe the different clinical situations and their impact on the nutritional status, the available substitution products, and the main points to consider for following an appropriate CMP elimination diet.

2. The nutritional risk in CMA

Scientific bodies increasingly highlight the importance of the assessment of physical growth in children with CMA [4–6].

2.1. Height and weight patterns of children with CMA

The growth deficit in children with proven CMA was identified in the early 1990s [4]. Growth may be affected by CMA before its recognition and treatment, and also during the elimination diet. In a Finnish nested case-control study, children on a milk elimination diet for at least 1 year had slower growth than healthy controls, with no catch-up growth by the age of 5 years [7]. Among Norwegian infants having followed a CMP-free diet for a median of 17 weeks, 10.5% had a weight z-score below −2.0 (Norwegian reference) and the same proportion had a Body Mass Index (BMI) z-score below −2.0 [8]. Finnish children with food allergy (FA) avoiding cow's milk alone or cow's milk and wheat were smaller, albeit not significantly, than their peers [9]. In the American National Health and Nutrition Examination Survey (NHANES), involving 6189 children aged 2–17 years, mean weight, height, and BMI percentiles were significantly lower in those with CMA [10]. Also in a large observational study conducted in the United States, children avoiding any form of cow's milk were smaller and lighter than healthy controls [11]. In 91 Italian children younger than 3 years with FA, 80 having CMA, 23% had a weight-for-length (WFL) z-score ≤ 2 versus 3% in healthy-matched children [12]; they also had significantly lower weight-for-age (WFA), length-for-age (LFA), and head circumference-for-age (HCA) z-scores. In Brazilian infants with a high suspicion of CMA, 16.5% were underweight, 27.8% stunted, and 13.9% wasted [13]. The impact of CMA on growth can also be seen in studies where the effect of CMA-adapted formula feeding was assessed [14]. Before starting feeding with an adapted formula, Italian infants with CMA had lower WFA z-scores than healthy controls [15]. In a large Dutch cohort of 119 children with CMA, 22.1% were underweight, 31.7% stunted, and 3.0% wasted [14]. In addition, between birth and enrollment at the age of 4.2 (± 1.4) months, the mean WFA z-score (based on WHO standards) significantly decreased from 0.3 (± 1.1) to −1.2 (± 1.2) [14]. Similarly, in 30 infants with CMA, mean WFA and LFA z-scores significantly decreased by 0.7 (± 1.0) and 0.6 (± 1.1), respectively, between birth and recruitment at a mean age of 4.8 (± 3.0) months [16]. Among the risk factors associated with poor growth (Table 1), the early onset of symptoms, before 6 months, might prevent the parents from increasing the amount of solid foods in the diet [17]. The frequent delay in CMA diagnosis increases the risk for undernutrition [18]. Improper food substitutions, such as the use of an extensively hydrolyzed protein-based formula (eHF) in an eHF-intolerant child results in continued low-grade antigen challenge and inflammation, a situation probably more frequent in children with multiple FAs [17,19]. As the number of weeks on a CMP-free diet was positively correlated with nutritional status [8], poor growth in CMA children could be due to persistent intestinal inflammation through reduction of nutrient absorption and/or increased requirements [20]. Despite nutrient intakes equivalent to those of the control population, French children with at least one FA, including CMA, still had growth retardation [21]. In children with CMA in the NHANE Survey, growth measurements remained low after adjustment for energy and nutrient intakes [10], and weight and BMI percentiles were lower than in healthy children who were not drinking milk.

2.2. Height and weight patterns of children with multiple FAs

Several studies suggested an increased deleterious effect on growth as the number of FAs increased. In the United States, allergy to two or more foods resulted in a lower HFA percentile than allergy to one food in 1-month- to 10-year-old children [22]. In 245 children aged 4.1 ± 2.9 years with real or perceived FA (peanut, hen's egg, then cow's milk), allergy to more than two foods was associated with lower weight and height percentiles than allergy to one or two foods [23]. In the UK, children with FAs aged 27 (0.5–149) months, the elimination of three or more foods was associated with a lower WFA z-score [24]. In Korean children with atopic dermatitis (AD), a higher number of FAs had a negative effect on growth [25]. In French children aged 4.7 ± 2.6 years with at least one FA (peanut, eggs then cow's milk) [21], allergy to three or more foods resulted in WFA and HFA z-scores ≤ 2 more frequently (14.5 and 12.1%) than in those with allergy to one or two foods (1.8 and 3.6%). These high figures in tertiary reference centers might relate to the more severe atopic population, since no effect was seen on height or weight in children avoiding more than one food in a general pediatric population [11].

2.3. Height and weight patterns of children with CMA compared to other FAs

CMA might be deleterious in itself. Weight and height deficits observed in children with CMA were not observed for other food allergies [11]. In the American cohort of children with real or perceived FA [23], cow's milk avoidance resulted in lower weight percentiles than avoidance of other foods. In the NHANE survey, mean weight, height, and BMI percentiles were lower in children with CMA but not in children with other FAs [10]. Recently, decelerated growth within the 1st year on the diet in children eliminating cow's milk was not observed in children eliminating wheat, barley, or rye [7]. In Japan, anthropometric indices were assessed at school age (7–15 years) in 11,473 children, among whom 3.6% had avoided food in the past due to allergic symptoms

Table 1
Risks factors associated with impaired growth in children with food allergy (issued from [18]).

(i)	Delayed diagnosis
(ii)	Onset of disease at an early age
(iii)	Multiple food allergies
(iv)	Active disease
(v)	Persistent (subclinical) inflammation of the gut resulting in increased requirements and/or losses and poor utilization of nutrients
(vi)	Inadequate food intake due to poor appetite, regulation of gastrointestinal symptoms by modifying diet
(vii)	Elimination of staple, nutritionally central foods from diet (milk, cereals)
(ix)	Poor compliance in dietary management (unwillingness to broaden diet variety)
(x)	Extreme self-restriction of foods