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Article

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Abstract: The diagnosis and management of cow's milk allergy (CMA) is a topic of debate and controversy. We aimed to compare the opinions of expert groups from the Middle East (n=14) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (n=13). These Expert groups voted on

statements developed by the ESPGHAN group and published in a recent position paper. The voting outcome was compared. Overall, there was consensus amongst both groups of experts. Most experts agreed that symptoms of crying, irritability and colic, as single manifestations, do not suggest CMA. They agreed that amino-acid-based formula (AAF) should be reserved for severe cases (e.g. malnutrition and anaphylaxis) and that there is insufficient evidence to recommend a step-down approach. There was no consensus on the statement that a cow's milk-based extensively hydrolysed formula (eHF) should be the first choice as a diagnostic elimination diet in mild/moderate cases. Although the statements regarding the role of hydrolysed rice formula as a diagnostic and therapeutic elimination diet were accepted, 3/27 disagreed. The votes regarding soy formula highlight the differences in opinion in the role of soy protein in CMA dietary treatment. Generally, soy-based formula is seldom available in the Middle East region. All ESPGHAN experts agreed that there was no added value of probiotics, prebiotics, and synbiotics to the efficacy of elimination diets, whereas 3/14 of the Middle East group thought there was sufficient evidence. Therefore, there is not a consensus on the optimal diagnostic and therapeutic elimination diet for CMA, but the first-choice elimination diet and the stepwise management approach reveal some differences. It can, therefore, be concluded that more data are needed to provide clear recommendations regarding the most adequate diagnostic elimination diet

Keywords: Cow's milk allergy; Infants; Extensively hydrolysed formula; amino acid-based formula; Soy formula; rice hydrolysed formula; probiotic; prebiotic; synbiotic

1. Introduction

Cow's milk allergy (CMA) is one of the most prevalent food allergies in infants and children under the age of three years [1–4]. CMA is an immune-mediated hypersensitivity response to several cow's milk (CM) proteins, mainly casein and lactoglobulin. The prevalence in Europe ranges from < 1% to 5%, while 3.4% is reported in the Middle East [5–9]. CMA can be IgE-mediated, non-IgE-mediated, or mixed. Depending on the type of immunological responses, the clinical manifestations are classified as immediate or delayed [9]. Making an accurate diagnosis followed by appropriate treatment is crucial to prevent over- and underdiagnoses and, consequently over- and undertreatment. This is a real challenge due to the lack of specific symptoms or an accurate diagnostic test [7,8]. Early diagnosis is a key factor, as delaying the diagnosis of CMA can lead to faltering growth and malnutrition [9].

An expert group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recently published consensus recommendations regarding diagnosing and managing cow's milk allergy in children [10]. Since food allergy and its management are significantly influenced by social contexts, eating habits, and available resources, this article aims to compare the opinions of a group of Middle East experts with those of ESPGHAN and thereby examine regional differences [12].

2. Materials and Methods

An ESPGHAN expert group (n=13) has developed a consensus paper on diagnosing and managing CMA [10,11]. This paper summarizes the most important findings and recommendations from systematic reviews and meta-analyses regarding CMA's prevalence, pathophysiology, symptoms, and diagnosis. The authors of the ESPGHAN voted on these statements [10], whereas a Middle-Eastern expert group (n=14) voted on 12 of the most important statements. Each statement was given a score from 1 to 9. A score of 6 or higher indicated agreement, while a score of five or less indicated disagreement. The higher the score, the greater the degree of agreement.

The votes of both expert groups were collected in a common file, analysed descriptively, and the median and mean were calculated. In addition to the range, the highest and lowest scores and the number of disagreements scoring five or less were provided.

3. Results

Most experts agreed that symptoms of crying, irritability and colic as isolated manifestations do not suggest CMA. Although both groups accepted the four statements regarding this topic, the Middle Eastern group was more in favour for colic as a possible symptom of CMA. The ESPGHAN authors strongly supported that colic, by itself, is not a symptom of CMA, and, therefore, were less supportive of a time limited elimination diet for infantile colic than the Middle Eastern group. In the latter there was 1 author with a disagreement for two statements. The results are presented in Table 1.

Table 1. Crying and infant colic.

| | Mean/Median Range (Number of disagreements) | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|------------------|
| | M East (n=14) | ESPGHAN (n=13) |
| In infants who present with crying and irritability, there is insufficient data to recommend a time-limited CM elimination diet followed by an OFC. | 7.6/8 5-9 (1) | 8.4/9 6-9 |
| There is insufficient data to support infant colic occurring as a single manifestation of CMA. | 6.7/8 1-9 (1) | 8.4/9 6-9 |
| When treatment for infant colic, fulfilling Rome IV clinical research criteria, is considered, and where CMA is suspected based on additional symptoms, a time limited elimination diet can be trialled which should be followed by an OFC. | 8.4/9 7-9 | 7.4/9 4-9 (1) |
| In patients not responding to conventional therapies for functional GI disorders (FGIDs), CMA can be considered and patients trialled on a time limited elimination diet which should be followed by an OFC. | 8.6/9 7-9 | 7.9/8 6-9 |

Regarding the diagnostic elimination diet, the Middle Eastern group reached a higher consensus than the ESPGHAN group, as seen in Table 2. Both groups recommend to restricting the use of amino acid formula (AAF) for severe cases, including patients with severe malnutrition, and therefore, do

not recommend a step-down approach, starting with AAF as a diagnostic elimination diet. Three out of the 27 experts from the combined groups, however, did not agree to recommend a cow's milk based extensively hydrolysed formula (eHF) as first choice for a diagnostic elimination diet. Similarly, three out of the 27 experts (2 from ESPGHAN and 1 from Middle East) disagreed to recommend rice hydrolysed formula (RHF) as an alternative first choice option for a diagnostic elimination diet. The rate of disagreement was similar for soy infant formula. Three out of the 27 experts (2 from ESPGHAN and 1 from Middle East) disagreed to recommend rice hydrolysed formula (RHF) as an alternative first choice option for a diagnostic elimination diet. It can, therefore, be concluded that more data are needed to provide clear recommendations regarding the most adequate diagnostic elimination diet.

Table 2. Diagnostic and therapeutic elimination diet

| | Mean/Median Range (Number of disagreements) | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|------------------|
| | M East (n=14) | ESPGHAN (n=13) |
| In formula fed infants, a CM based extensively hydrolysed formula (eHF) is the first choice for a diagnostic elimination diet in mild/moderate cases. | 8.1/8.5 4-9 (1) | 7.2/9 0-9 (2) |
| In formula fed infants, amino acid-based formula (AAF) for a diagnostic elimination diet should be reserved for severe cases or patients with severe malnutrition. | 8.3/8.5 6-9 | 8.5/9 7-9 |
| Although some consensus papers recommend a step-down approach using AAF as diagnostic elimination diet in every infant suspected of CMA, there is insufficient evidence for this recommendation. | 8.0/9 6-9 | 8.6/9 6-9 |
| Although less studied than CM based eHFs, rice hydrolysed formulae (RHF) can be considered as an alternative for a diagnostic elimination diet. | 8.1/9 5-9 (1) | 7.4/8 1-9 (2) |
| Soy infant formula should not be used as the first choice for diagnostic | 8.0/9 5-9 (1) | 7.6/9 0-9 (2) |

| | | |
|-----------------------------------------------------------------------------------------------------------------|--------------|------------------|
| elimination diet but can be considered in some cases for economic, cultural and palatability reasons. | | |
| Rice hydrolysed formula can be considered as an alternative to CM based eHF for a therapeutic elimination diet. | 8.2/9 6-9 | 7.8/8 5-9 (2) |

The statement regarding the absence of an added therapeutic efficacy of probiotic, prebiotics and synbiotics to eHFs and AAFs was accepted by all European authors but was rejected by 3/14 Middle Eastern authors.

Table 3. Pro-, pre- and synbiotics.

| | Mean/Median Range (Number of disagreements) | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------|
| | M East (n=14) | ESPGHAN (n=13) |
| There is insufficient evidence demonstrating that the addition of probiotics, prebiotics or synbiotics to eHFs and AAFs improves their therapeutic efficacy. | 6.6/8 1-9 (3) | 8.9/9 9 |

4. Discussion

Overall, all statements were accepted by both groups of experts. However, some key differences were observed. Several organisations, such as The British Society for Allergy & Clinical Immunology (BSACI), The World Allergy Organisation and ESPGHAN encourage the development of region-specific guidelines that meet the needs of children from all social strata in the targeted countries [11–14].

CMA symptoms and indicators include cutaneous, gastrointestinal, respiratory, and systemic responses. IgE mediated CMA's clinical symptoms appear "immediately" and occur within minutes to two hours. In a non-IgE-mediated immune reactions, the appearance of symptoms is "delayed", and develop usually after ≥ 2 hours up to one week after exposure [10,15]. Most experts in both groups agreed that symptoms of crying, irritability and colic as single manifestations are not suggestive of CMA. However, the Middle Eastern experts tended to consider CMA as a cause of infant distress and colic compared to the European authors.

The diagnosis of CMA is based on a thorough history and physical examination. A diagnostic elimination of CM protein for one to four weeks followed by an oral food challenge or reintroduction of CM is advised when CMA is suspected [10].

In non-exclusively breastfed infants suspected to suffer from CMA, a formula with reduced allergenicity for CM is recommended. However, formula selection is controversial and frequently influenced by availability, economics factors and scientific evidence [1,2,12,16]. At the current time, evidence is strongest for the using a CM-based eHF for the diagnostic elimination diet. The combined groups, however, failed to reach unanimous consensus on the use of eHF as the first-choice diagnostic elimination diet", given that 3/27 authors disagreed. One rationale for recommending eHF as the first-line formula is the higher cost of AAF in the majority of countries [17]. Nonetheless, some studies have found AAF to be comparable or more cost-effective [12], and recommend a step-down

approach. Consequently, there is a need for international guidelines to be adapted to national recommendations that take into consideration the local health system [16].

The statement that AAF should be reserved for severe cases or patients with serious malnutrition was accepted by both expert groups. A recent review by Ribes-Koninckx et al. confirms this statement. It suggests using AAF when treatment with eHF is unsuccessful or in the case of severe CMA, particularly with associated nutritional deficiencies [3]. IgE-mediated anaphylaxis associated with CMA, acute and chronic food protein induced enterocolitis syndrome (FPIES), multiple food allergies associated with CMA, and eosinophilic esophagitis unresponsive to a prolonged exclusion diet are a few examples [3]. Five to ten percent of children with an IgE-mediated CMA react to eHF[2,3]. AAF, compared to eHF, does not contain immunogenic peptides that stimulate the immune system. Due to these negative factors, CMA and the use of AAF must be frequently re-evaluated. The patient's age at diagnosis, symptoms, serum IgE level, and nutritional status are involved in this reassessment [3].

Some recommendations propose a step-down strategy. In this case, AAF is used as a diagnostic elimination diet. Subsequently, an eHF is used as the therapeutic elimination diet when the OFC or reintroduction causes a relapse of symptoms. However, this approach is not frequently used, mainly for economic reasons [10].

In Europe, formulas containing hydrolysed rice protein (HRF) have been commercially available since the 2000s as a nutritionally acceptable and well-tolerated plant-based alternative to eHF [2]. Access to and availability of HRF are the primary factors limiting its global usage; eHFs and AAFs are the two most accessible types of substitute formulas [12]. In addition to regional differences, there are differences in usage between specialists and non-specialists [2]. This difference could not be demonstrated in the current manuscript because opinions of non-specialists were not collected.

One advantage of HRF is that it has a better flavour than eHF. In addition, it does not contain any residues of CM protein [1]. In contrast, concerns have been raised regarding the arsenic content of infant rice products [18]. Arsenic can be found in small amounts in rocks, soil, and groundwater, both inorganic and organic forms[19]. Consequently, exposure during infancy may have potential long-term health effects, like an increased risk for developing pulmonary disease and cancer in adulthood [19,20]. Since 2016, the European Union has set a maximum concentration of 0.10 mg/kg for inorganic arsenic in rice intended for infants under the age of three[21]. Hojsak et al. concluded that the arsenic concentration in HRF is low and well within the safe range established by the European Food Safety Authority, with no significant difference compared to the arsenic concentration in cow's milk formulas [19,22]. However, it should be noted that not all commercially available HRF list the arsenic content on their labels [23]. The arsenic concentration in water used to prepare the formulae, will also contribute to final arsenic content. Despite the paucity of data, the statements regarding a role for HRF as a diagnostic elimination diet were accepted by both expert groups.

[Soy formula may also be a treatment option, but limited evidence supports its usage[10]. Current soy infant formulae are nutritionally adequate and promote healthy growth and development. In the first two years of life, soy infant formula does not reduce the likelihood of allergic manifestations [24,25]. Cross-allergy between CM protein and soy is rare in IgE-mediated CMA; therefore, soy-based infant formula can be used as an alternative therapy diet [26,27]. However, it should be noted that cross-allergy is more prevalent in non-IgE-mediated CMA. The majority of data supporting this association originate from the United States. Studies conducted in the US indicate that 30 to 50% of children with FPIES react to both cow's milk and soy, while the overwhelming majority of studies originating from outside the US indicate a much lower percentage [10,28]. Soy allergy prevalence ranges from 0 to 0.5% in the general population and 0 to 12.9% in allergic children [29]. The availability of soy infant formula in many European countries has decreased in recent years. Soy infant formula can be considered as a second option when other formulae are not possible due to economic or cultural factors. Additionally, soy infant formula has a more favourable flavour and is cheaper compared to eHF[10].

CMA is associated with intestinal dysbiosis, with reduced diversity of gut microbiota as well as a low abundance of Bifidobacteria, Lactobacilli and Bacteroides [30]. Modulating the intestinal microbiome may be a valuable management strategy for CMA. Adding pre-, pro-, syn-, or postbiotics to infant formulae could be one way to reach this goal [31]. Several hypoallergenic formulations include pre-, pro-, syn- or postbiotics. However, due to a lack of evidence-based literature, their additional efficacy in CMA has not yet been established [3,31]. All ESPGHAN experts agreed there was no added value of prebiotics, probiotics and synbiotics in the efficacy of elimination diets, whereas 3 of the 14 authors of the Middle Eastern group thought there was evidence.

The 2021 Middle East Consensus Statement described that adding prebiotics and synbiotics to a therapeutic formula may improve the tolerance to CM protein by the end of the first year of life [9]. Synbiotics can improve gut microbiota in non-IgE-mediated CMA, bringing it closer to that of a healthy newborn [9]. Sorensen et al. described in their systematic review that combining synbiotics and AAF resulted in the same reduction of allergic symptoms and average growth as AAF alone [31]. In addition, outcomes suggest that the observed combination of improved dysbiosis and a trend toward decreased infection, hospital admissions, and antibiotic use might be due to the intestinal microbiome's essential role in maintaining health and disease development [31,32]. Several studies have demonstrated that antibiotic use in children aged 0 to 3 causes a less diverse microbiome, with a reduced abundance of Bifidobacteria, Lactobacilli and Bacteroides [30,33]. Because of these negative effects on the gut microbiome, antibiotic exposure during the first years of life is associated with an increased risk of developing hay fever, eczema, and food allergy later in life, according to a 2018 meta-analysis [34]. Metsala et al. concluded that antibiotic use in children was associated with an increased risk of developing CMA [35]. A study encompassing 30060 children up to 7 years of age, revealed that children who received three or more antibiotic treatments were more likely to develop milk allergy, non-milk food allergy and other allergies compared to children who did not receive antibiotics. The strongest associations were observed at lower ages and varied by antibiotic class [36]. Overall, using probiotics during and after an antibiotic course may reduce the harmful impact of antibiotics on the gut flora [34]. This could ultimately result in an economic advantage with lower costs [31].

Several additional studies showed that the addition of *Lactocaseibacillus rhamnosus* GG (LGG) is a cost-effective CMA treatment. In the United States, Guest et al. found that adding LGG to eHCF was a more cost-effective strategy than eHCF alone or AAF, as it improved outcomes at a lower cost [37]. A Spanish investigation revealed comparable results [38]. A study by Martin et al. indicates that eHCF combined with LGG is the most cost-effective strategy for treating CMA in the United Kingdom [39]. According to a French study by Paquete et al., the combination of eHCF and LGG was associated with longer symptom-free periods, greater immune tolerance, and reduced costs [40].

An important limitation of this report is that only the opinion of selected experts was solicited. Gathering input from a broader range of professionals such as general paediatricians, family doctors, allergologists, dietitians, and parents, could provide a more comprehensive perspective on how CMA is addressed in clinical practice. Expanding this analysis to a larger population may uncover more noticeable differences between cultures and regions.

5. Conclusions

CMA comprises a broad spectrum of symptoms and indicators of varying severity. Because of the limited evidence, some experts differ in opinion regarding the role of crying, irritability, and colic in CMA. The optimal diagnostic and therapeutic elimination diets are still debated as well. This emphasizes the importance of developing excellent region-specific guidelines based on the available resources. The approach in CMA should consider the child as an individual, based on clinical contexts. Furthermore, it is essential to consider the social context to ensure that the needs of children from all social strata within specific countries are met. Moreover, access to medical services and the availability of CMA-free diet must be considered. Emphasis should be made on timely and accurate diagnosis to prevent complications such as growth and developmental issues. Lastly, this study highlights the fact that many current guidelines, including guidelines on CMA, are often based on

expert opinion. Knowledge about CMA has increased over the past few decades, however, the study presented here underscores that there is still much work to be done. Through identifying and highlighting discrepancies among expert groups, we have pinpointed research priorities in this area, such as the potential added value of probiotics, prebiotics, and synbiotics for the efficacy of elimination diets. By making substantial progress in these areas over the next few years, we believe we can promote the health and well-being of children suspected of having CMA in the future.

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