Clinical and follow up assessment of children in a program directed at the use of formulas for cow’s milk protein allergy

Avaliação clínica e evolutiva de crianças em programa de atendimento ao uso de fórmulas para alergia à proteína do leite de vaca

Evaluación clínica y evolutiva de niños en programas de atención al uso de fórmulas para alergia a la proteína de leche de vaca

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ABSTRACT

Objective: To determine clinical and follow up characteristics of children enrolled in a program to supply formulas for cow’s milk allergy.

Methods: descriptive study of a convenience sample composed of 214 children up to three years old, with clinical diagnosis of cow’s milk allergy and/or standardized oral challenge, referred to the Program of Formulas for Cow’s Milk Allergy at a Pediatric University Hospital, in Natal, Rio Grande do Norte, Brazil (2007/2009). Clinical-epidemiological data and formula indication (soy, protein hydrolysates or aminoacid formula) were assessed at the first consultation. Clinical response and nutritional evolution (Anthro-OMS2006) were observed after three months. Chi-square and paired t-test were used, being \(p<0.05\) significant.

Results: At the first consultation, mean age was 9.0±6.9 months. Digestive manifestations occurred in 81.8%; cutaneous ones, in 36.9% and respiratory ones in 23.8%. BMI Z-score <-2.0 standard deviations (SD) was found in 17.9% of children with isolated digestive symptoms, in 41.7% of those using cow’s milk and in 8.7% of those using other formulas (\(p<0.01\)). The following formulas were used: soy in 61.2%, protein hydrolysates in 35.4% and aminoacids in 3.3%. Mean BMI Z-scores at initial consultation and after three months were, respectively: -0.24±1.47SD and 0.00±1.26SD (\(p=0.251\)), with soy formula, and -0.70±1.51SD and -0.14±1.36SD (\(p=0.322\)) with protein hydrolysates formula.

Conclusions: Digestive manifestations of cow’s milk allergy were preponderant, and lead to greater nutritional impairment. The use of replacement formulas (isolated soy protein and protein hydrolysates) was important to maintain the nutritional status.

Key-words: milk hypersensitivity; diet therapy; milk substitutes; programs; soy milk; child.

**Resultados:** Ao primeiro atendimento, a média de idade foi de 9,0±6,9 meses. Manifestações digestórias foram observadas em 81,8%; cutâneas, em 36,9%; e respiratórias, em 23,8%. Escore Z do IMC <-2,0 desvios padrão (DP) foi encontrado em 17,9% das crianças com sintomas digestórios isolados, em 41,7% em uso de leite de vaca e em 8,7% com outras fórmulas ($p<0,01$). Fórmula de proteína isolada de soja foi usada em 61,2%; hidrolisados, em 35,4%; e aminoácidos, em 3,3%. As médias de escore Z do IMC ao atendimento inicial e após três meses foram, respectivamente, $-0,24±1,47DP$ e $0,00±1,26DP$ ($p=0,251$), quando em uso de soja, e $-0,70±1,51DP$ e $-0,14±1,36DP$ ($p=0,322$), em uso de hidrolizado.

**Conclusões:** Manifestações digestórias da alergia ao leite de vaca foram preponderantes e determinaram maior comprometimento nutricional. As fórmulas de substituição ao leite de vaca mais utilizadas foram de proteína isolada de soja e hidrolizados proteicos. O uso de ambas foi importante para a manutenção do estado nutricional.

Palavras-chave: hipersensibilidade a leite; dietoterapia; substitutos do leite; programas; leite de soja; criança.

**RESUMEN**

**Objetivo:** Determinar características clínicas y evolutivas de niños acompañados en programa de referencia para suministro de fórmulas especiales para alergia a la leche de vaca.

**Métodos:** Estudio descriptivo, realizado en muestra de conveniencia, con 214 niños hasta tres años de edad, con diagnóstico clínico y/o prueba estandarizada de provocación oral abierta, referenciadas al Programa de Fórmulas para Alergia a la Leche de Vaca del Hospital Universitario Pediátrico en Natal, RN, Brasil (2007/2009). Se evaluaron datos clínico-epidemiológicos e indicación de fórmulas (soja, hidrolizado o aminoácido) a la consulta inicial, respuesta clínica y evolución nutricional (Anthro-OMS 2006) después de tres meses. Se aplicaron pruebas de Chi-Cuadrado y T Pareada en los análisis, siendo significante $p<0,05$.

**Resultados:** A la primera atención, el promedio de edad fue de 9,0±6,9 meses. Manifestaciones digestarias fueron observadas en 81,8%, cutáneas en el 36,9% y respiratorias en el 23,8%. Escore Z IMC <-2,0DE fue encontrado en 17,9% de los niños con síntomas digestarios aislados, en el 41,7% en uso de leche de vaca y en 8,7% en otras fórmulas ($p<0,01$). Se utilizó fórmula de proteína aislada de soja en 61,2%, hidrolizados en 35,4% y aminoácidos en 3,3%. Promedios de Escore Z IMC a la atención inicial y después de tres meses fueron $-0,24±1,47DE$ y $0,00±1,26DE$ ($p=0,251$), cuando en uso de soja, y $-0,70±1,51DE$ y $-0,14±1,36DE$ ($p=0,322$), en uso de hidrolizado.

**Conclusiones:** Manifestaciones digestarias de la alergia a la leche de vaca fueron preponderantes y determinaron mayor comprometimiento nutricional. Las fórmulas de sustitución a la leche de vaca más utilizadas fueron de proteína aislada de soja e hidrolizados proteicos y el uso de ambas fue importante para el mantenimiento del estado nutricional.

Palabras clave: hipersensibilidad a la leche/dietoterapia; sustitutos de la leche/programas; leche de soja; niño.

**Introduction**

Cow’s milk protein (CMP) has high allergenic potential and is considered the most common cause of food allergy(1). The diagnosis of cow’s milk protein allergy (CMPA) is based on clinical manifestations, response to elimination diet and subsequent double-blind, placebo-controlled food challenge test (gold standard)(2). However, due to its practical difficulties, an open challenge test(3-5) is usually used as the first step. After confirmation, further tests are recommended every 6 to 12 months, due to the possibility of development of tolerance, especially in the first 3 years of life. Thus, the elimination of food for longer than necessary is avoided(4). Its treatment consists in removing the CM and its derivatives from the diet and replacing them with formulas based on soy protein isolate, extensively hydrolyzed protein, or amino acids, depending on clinical criteria(6).

Data concerning the prevalence of CMPA are scarce, and it is difficult to confirm its diagnosis, since clinical manifestations are varied, affecting the digestive and respiratory systems and the skin, and can be confused with other food hypersensitivities. Furthermore, oral challenge tests for clinical diagnosis are still little used in practice.

Due to the high cost of hypoallergenic formulas used to replace CM, some government programs were implanted in...
the country in recent years, through isolate initiatives, to evaluate the indication of such formulas, with the goal of minimizing their unnecessary use and reduce the financial resources allocated to them, as well as nutritional risks arising from an inadequate indication.

The scarcity of publications in the country presenting analysis of case studies arising from these programs motivated the study, which can bring a contribution to the implementation and/or management of similar programs, in different regions, and the consequent adoption of strategies for the management and treatment of CMPA. Thus, the aim of this study was to determine the clinical, epidemiological, dietary, and outcome characteristics of patients referred to the Program for the Assessment of Indication and Use of Infant special formulas for Cow’s Milk Protein Allergy (Programa de Avaliação da Indicação de Fórmulas Infantis Especiais para Alergia à Proteína do Leite de Vaca - PAIUFA), implemented in 2007, at Hospital de Pediatria da Universidade Federal do Rio Grande do Norte (Hosped-UFRN), a reference service in the state.

Method

The present study was developed at Hospital de Pediatria da Universidade Federal do Rio Grande do Norte between January 2007 and December 2009. The convenience sample consisted of 214 children aged 0-3 years, living in the state of Rio Grande do Norte, treated at the units of the Brazilian public Unified Health System (Sistema Único de Saúde - SUS) or at the private sector and referenced to the PAIUFA by physicians or nutritionists for presenting symptoms attributed to the ingestion of CMP.

The study assessed all children treated in the study period who received permission to obtain formulas for CMPA from at least one of the three pediatric gastroenterologists within the Program, who filled a specific questionnaire, with or without performing open oral challenge test (OCT) at the service. The test was considered positive with the reappearance of immediate or late signs and symptoms compatible with CMPA after the reintroduction of CM in the infant’s diet. For those who were not subjected to the OCT, the analysis considered clinical evidence after the introduction of CM and the resolution of signs and symptoms with the elimination diet (4,5).

The OCT was not performed in cases of previous severe immediate reactions (characterized by major vomiting and wheezing, breathing difficulties, severe hives, angioedema, anaphylaxis, and food protein-induced enterocolitis syndrome, occurring within minutes until 2 hours after exposure to CM), peremptory refusal of family, in children with nutritional diagnosis of thinness and accentuated thinness, or those who had already been through a procedure observed by a pediatrician companion.

In the questionnaire, epidemiological and clinical data were recorded, such as age, sex, origin, referral, (SUS or private practice), gestation, family, and food history, symptomatology, and type of formula given.

At follow up, the clinical response of patients, dietary conduct (maintenance, replacement or suspension of the formula) and the evolution of the nutritional status were assessed 3 months after the first consultation. Reference standards of WHO-2006 were used to assess the nutritional status, from the analysis of the BMI Z-score (7). For the classification of nutritional status, given the cutoff values, the children were grouped into two groups, namely: BMI Z-score < -2.0SD and BMI Z-score ≥ 2.0SD. Data were assessed by the program WHO-Anthro 2006.

The data processing and statistical analyses were performed using the SPSS software, version 17.0. In order to compare the variables between different groups, the sample was stratified by age (<6, ≥ 6 and <12, ≥12 months), sex, nutritional status (BMI Z-score < -2.0SD = thinness or severe thinness, BMI Z-score ≥ -2.0SD = normal weight, overweight or obese), clinical manifestations (cutaneous, respiratory or digestive, isolated or associated) and kind of formula used (based on soy protein isolate, protein hydrolysate, or amino acid). The chi-square test or Fisher’s exact test were used to compare proportions and the paired t-test to compare the nutritional status of individuals before and after the dietary intervention, after confirming the normality of this variable through quantitative Kolmogorov-Smirnov Test. The level of significance was set at 5% (p < 0.05).

The study was approved by the Research Ethics Committee of Hospital Universitário Onofre Lopes/UFRN, under protocol number 218/08. All parents or guardians signed the Consent Form.

Results

The present study evaluated 214 children with mean age of 9.0 (±6.9) months at the first treatment, being 58.4% male, and 41.6% female; 68.1% from the municipality of Natal and 31.9% from other cities in the state; 59.4% from private health service and 40.6% from public health service.

The mean age of onset of symptoms was of 2.8±2.5 months, with a mean of introduction of CM of 2.6±2.3 months and median of 2 months. Although suffering from signs and

symptoms involving different systems simultaneously, isolated manifestations of the digestive system, skin, and respiratory tract were found in 49.5, 11.2 and 2.3%, with mean age of onset of symptoms of 2.0±1.9 months, 3.3±2.3 months, and 4.0±3.0 months, respectively. Figure 1 discriminates symptoms most frequently encountered and overall percentage of involvement of the respiratory system, digestive tract, and skin.

The assessment of nutritional status by BMI z-score showed thinness or severe thinness in 12.9%, normal weight in 67.8%, risk of overweight in 15.2% and overweight or obesity in 4.1%.

At arrival at the service, the percentage of children using CM, soy-based, protein hydrolysate, or amino acid formula was 10.5%, 65.1%, 19.8% and 4.7%, respectively. Among those using CM (n=12), thinness (BMI Z-score<-2.0SD) or

![Figure 1 - Main signs and symptoms according to systems affected in children treated at the PAIUFA/Hosped-UFRN (Program for the Assessment of Indication and Use of Infant special formulas for Cow’s Milk Protein Allergy), from January 2007 to December 2009](image)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Respiratory</th>
<th>Digestive</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total respiratory</td>
<td>23.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>9.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>12.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>1.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itch</td>
<td>7.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total skin</td>
<td>36.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>18.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hives</td>
<td>20.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total digestive</td>
<td>81.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>13.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>31.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood in stools</td>
<td>34.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Table 1 - Indication of infant special formulas at first consultation of children at the PAIUFA/Hosped-UFRN (Program for the Assessment of Indication and Use of Infant special formulas for Cow’s Milk Protein Allergy), from January 2007 to December 2009](table)

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Soy</th>
<th>Protein Hydrolysate</th>
<th>Amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>0 to 6 (n=96)</td>
<td>43</td>
<td>44.8</td>
<td>48</td>
</tr>
<tr>
<td>6 to 12 (n=60)</td>
<td>42</td>
<td>70.0</td>
<td>17</td>
</tr>
<tr>
<td>≥12 (n=58)</td>
<td>46</td>
<td>79.3</td>
<td>11</td>
</tr>
</tbody>
</table>

![Table 2 - Digestive, skin, and respiratory involvement in children treated at the PAIUFA/Hosped-UFRN (Program for the Assessment of Indication and Use of Infant special formulas for Cow’s Milk Protein Allergy), from January 2007 to December 2009, by age group](table)

<table>
<thead>
<tr>
<th>Age group (in months)</th>
<th>Digestive</th>
<th>Cutaneous</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>0 to 6 (n=96)</td>
<td>81</td>
<td>84.4</td>
<td>25</td>
</tr>
<tr>
<td>6 to 12 (n=60)</td>
<td>49</td>
<td>81.7</td>
<td>24</td>
</tr>
<tr>
<td>≥12 (n=58)</td>
<td>44</td>
<td>75.9</td>
<td>30</td>
</tr>
</tbody>
</table>

severe thinness (BMI Z-score < -3.0SD) were found in 41.7% (n=5) and among those using other formulas (n=126), in 8.7% (n=11) (p=0.001). Children with isolated manifestations of the digestive system showed thinness or severe thinness at 17.9%, which was not found in any child with isolated involvement of the respiratory system or skin.

The formulas indicated or maintained at the first visit to the PAIUFA, regardless of the age of the child, were soy protein isolate formulas in 61.2% of cases, protein hydrolysate in 35.4% and amino acid in 3.3%. Table 1 shows the formulas prescribed in accordance with the age of the sample. The frequency of symptoms distributed according to age is presented in Table 2.

For individuals who presented exclusively digestive symptoms, formulas based on soy protein isolate were prescribed in 51%, protein hydrolysate in 43.3% and amino acid in 5.8%. For those with cutaneous symptoms only, formulas based on soy protein isolate were prescribed in 78.3% and protein hydrolysate in 21.7%, with no observed prescription of amino acid formulas. All children with only respiratory symptoms were prescribed formula based on soy protein isolate.

Among the 214 patients, 63 (29.4%) underwent oral challenge test at some point in medical monitoring. Among these, 59 (93.6%) had positive response within 4 weeks after challenge, two (3.2%) in the 5th week, manifested by recurrence of clinical manifestations, and two discontinued follow-up after the 1st month of observation following the OCT. Among the 151 patients who did not undergo the OCT, the most prevalent reasons were: history of previous challenge well established (29.8%), previous severe immediate reactions (29.2%), thinness or severe thinness (17.2%), refusal of doing the procedure by family members (15.2%) and not returning for follow-up on schedule (8.6%). Some children had more than one factor.

Of the total sample, 62.1% returned for reevaluation after 3 months. Among those on soy protein isolate formula (n=91), prescription was maintained in 83 (91.2%), replacement in seven (7.7%) – all for the protein hydrolysate – and suspension occurred in one case (1.1%). Among those using protein hydrolysate (n=37), the formula was maintained in 30 (81.1%), replaced in six (16.2%) – five to soy protein isolate formula and one to amino acid formula - and suspended in one (2.7%). For children in the use of amino acids (n=5), the formula was maintained in one, replaced in three (all for protein hydrolysate), and suspended in one.

Table 3 shows the evolution of the nutritional status of children, when assessed after 3 months using soy formula or protein hydrolysate. Because of the smaller number of children using amino acid formula, the analysis of these data was compromised. The mean BMI Z-scores of children in use of soy formula at the first visit and after 3 months were -0.24 ± 1.47SD and 0.00 ± 0.26SD, respectively (p=0.251). For those using protein hydrolysate, the means were -0.70 ± 1.51SD and -0.14 ± 1.36SD (p=0.322).

Discussion

PAIUFA is the current reference in the state of Rio Grande do Norte for children with proven or suspected diagnosis of food allergy, with emphasis to the CMPA. Since its creation, there was a sharp increase in this demand at the Hosped-UFRN. In this sense, it is important to know the epidemiological and clinical characteristics of the clientele, bringing support for new diagnostic, interventionist, and preventive actions.

Observing the mean age at first consultation at the PAIUFA and the ages of onset of symptoms suggestive of CMPA, there is an interval of approximately 6 months. This may be related to previous diagnosis difficulties, late referral to the service or the previous use of special formulas prescribed by companions and acquired through the family’s resources.
The median of introduction of cow’s milk (2 months) reflects the highly precocious presence of this allergen on children’s menu, at a moment that is fully compatible with exclusive breastfeeding, being a high-risk condition for the emergence of CMPA. In exclusive breastfeeding, such exposure could be postponed to a more appropriate moment.

The prevalence of clinical manifestations of CMA depends on the sample from different services such as pneumo-allergology, gastroenterology, and dermatology. However, the prevalence of digestive symptoms in the PAIUFA highlights the importance of the digestive involvement, such as in other studies, since the program is a reference available to all professionals and specialties allegedly involved with CMPA.

Among the manifestations suggestive of CMPA that prompted the referral to the program, diarrhea was the most prevalent digestive manifestation (51.9%), however, constipation was found in 8.9%, which calls attention to this newly recognized form of presentation of CMPA. Allergic colitis, evidenced by the presence of blood in stools, and included among the phenomena of CMPA, was found in 34.6%. Despite the prevalence of hives (20.1%) in this study, there is growing relevance of cases of atopic dermatitis (AD) as a manifestation of food allergy, which was found in 18.2%.

When children with exclusive involvement of the digestive and respiratory systems or the skin were compared, in relation to their nutritional status, thinness was found exclusively in individuals whose digestive system was affected, which may reflect the participation of the malabsorptive component in this process. It is interesting to note that children who came to the health facility still using cow’s milk had higher percentages of thinness or severe thinness than those whom no longer used that component on their diets, replacing it with other formulas.

Among children evaluated in the program, 83.1% were already using special formulas, based on soy, protein hydrolysate, or amino acid, at first consultation. Around 50% performed the challenge test for confirmation of the CMPA, either before (observed by the family doctor) or after the arrival to this service (during monitoring).

Despite the recommendation of the OCT for the clinical diagnosis of CMPA, this procedure has several objections in daily clinical practice, which leads it to be performed below the expectation. The percentage of children who took the test in the present study reflects difficulties by the pediatrician in referring it. Children with CMPA on elimination diet and use of appropriate formulas, when malnourished, undergo a process of weight gain (and, subsequently, height). To interrupt it for an early challenge test, in a few weeks, strictly with diagnostic purposes, is perhaps questionable, because it takes them to previous levels, with new impairment to growth and development. Likewise, there are clinical situations in which the obligation of OCT is disregarded, such as in those with more immediate manifestations, particularly those mediated by IgE, according to a recent publication by Koletzko et al. Exposing patients to new and serious risks may be dispensable. It is noteworthy that the PAIUFA does not impose the TPO at the hospital as a sine qua non condition to deliver special formulas, despite recommending it to every assistant doctor and doing it when the situation is appropriate. However, most doctors do not have the physical structure for a safe execution of the procedure. We must consider also the ethical, legal, and professional issues related to performing OCT in patients who are referred to the programs, but who are actually monitored by their doctors of origin and arrive at the service already with the diagnosis established, in order to receive formulas due to their high cost. Accepting this responsibility is doubly compromising due to the risk of producing unexpected reactions and of not treating the patient, with implications still unclear. Moreover, there are family members who strongly refuse the procedure, because their children are well on the diet. These considerations are difficult to solve and still subject to omission from debate. For all the above reasons, it is assumed that a proportion of children remain on exclusion diets without definitive proof of CMPA. Therefore, the rigidity of the main diagnostic tool, be it the open, blind or double-blind OCT, makes it underused in practice and open to discussion, despite the extreme appreciation of its theoretical precepts.

The percentage of prescription or maintenance of formulas at the first appointment are certainly influenced by prior prescription by professionals responsible for referral, calling attention to the extensive use of formulas based on soy protein isolate, despite the fact that the PAIUFA does not indicate the prescription of these formulas for children under six months, the evidence of their allergenic potential, and the controversies regarding estrogen stimulation and carcinogenesis. However, its use was higher in children older than 6 months. On the other hand, higher rates of prescription of protein hydrolysate and amino acid formulas occurred to those under 6 months, in which predominated digestive manifestations, when compared to skin and respiratory conditions.
and close observation of these individuals in relation to their nutritional status and other manifestations of intolerance for a longer period, will allow better understanding of these findings, when compared to children using the different formulas. However, the new guidelines from ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) in 2012, are more flexible in their use of isolated soy protein after the first 6 months of life, not only in the form of IgE-mediated CMA, but also in manifestations of the digestive system, as an alternative to protein hydrolysate, still considered the first option. The authors observed low percentages of soy intolerance (10–14%), over the previous statistics considered the first option. The authors observed low percentages of soy intolerance (10–14%), over the previous statistics considered the first option.

It should be mentioned the high cost of the formulas for intervention, so its efficacy, safety, cost-benefit, and indication in different age groups should be prioritized. Government programs for the acquisition and supply of special formulas for CMPA, to be deployed or in progress, as well as health services that serve these clients should know the profile of their target audience or similar case studies that can assist in planning clinical interventions, dietary interventions, and application of resources in an appropriate and balanced manner.

The evidence of the early symptoms of CMPA reinforces the importance of encouraging exclusive breastfeeding in the first 6 months of life and its maintenance until 2 years, as the main prevention strategy. Despite the cutaneous and respiratory involvement in CMPA, the symptoms of the digestive system have prime importance due to its high frequency and adverse effects on nutritional status. The use of protein hydrolysate is a priority, as a replacement diet for children with CMPA, but the formulas of soy protein isolate still constitute a favorable alternative, especially for those over 6 months of life. The amino acid formulas should be restricted to cases of intolerance to hydrolysate, multiple allergies or severe clinical conditions with intense nutritional deficits.

References

   http://nutricao.saude.gov.br/sisvan.php?conteudo=curvas_cresc_oms