The many faces of Cow's Milk Allergy

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Take Home message

• Cow milk allergy: Ig E mediated
• Potential Anaphylaxis
• Cow milk Intolerance: Non IgE
  • Eczema
  • Blood in stools
  • Irritability
• Lactose intolerance: low lactase associated with diarrhoea and irritability
• Cow's milk protein is hydrolysed to decrease allergenicity which works for Allergy and intolerance.
• Treatment options: EHF, ERHF, Soy, AAF

Cow's Milk Allergy

• Babies are not Calves

Cases 1: Unsettle baby

• 8 week old
• Crying, very unsettled
• Breast fed
Case 2: Eczema

- Severe eczema over the body
- 2 months of age
- Breast fed

Case 3: Crying, possetting

- 2 months of age
- Bottle feeding

Case 4: Blood in stools

- 4 week old
- Breast fed

Australia consensus statement

Cows milk protein allergy syndromes

- Immediate allergic reactions
- Food protein-induced enterocolitis syndrome (FPIES)
- Atopic eczema
- Gastrointestinal syndromes
- Gastro-oesophageal reflux disease (GORD)
- Allergic eosinophilic gastroenteritis
- Food protein-induced enteropathy
- Constipation
- Severe irritability (colic)
- Food protein-induced proctocolitis
- Eosinophilic oesophagitis
Preparations available for treating cows milk protein allergy

• Soy formulas,
• Extensively hydrolysed formulas, Alfare (Nestlé), Pepti-Junior (Nutricia),
• OTC Allerpro (prebiotics)
• Amino acid formulas EleCare (Abbott), Neocate (SHS), Alphamino (Nestle)
• Extensive Hydrolysed Rice formula Novumac (OTC)
• Not recommended
• Formulas: Cows milk-based (including anti-regurgitation),
• Lactose-free cows milk-based
• Partially hydrolysed cows milk-based
• (eg, Karicare SensiKare [Nestlæ]), NANN HA [Nestlæ])
• Goat milk-based formula
• Other preparations A2 milk (A2 Australia) Rice milk, Oat milk
• Other mammalian milks (camel, mare, ass, goat and ewe)

Soy formulas effect on puberty

7 co-twin marmoset monkeys fed Soy vs CM formula and study the testosterone levels, testicle side, adult onset of puberty

• Results:
  • no difference in puberty onset
  • testicular weights and No.sertoli and Leydig cells number increased.
  • Testosterone rise levels were suppressed in soy group,
  (Leydig cell failure)
  • Average of 26% increase in seminiferous epi volume per tubules/ tests.
• Conclusion:
  • exposure to soy formula should be reserve for > 6 months of age.

Soy Milk: Phytoestrogen

• Isoflavones a class of phytoestrogen can bind to estrogen receptors and exert estrogenic activity
• Levels:
  • soy: 18-47kg/L
  • Cow Milk: 0.1-5kg/L
  • Breast milk: 1.6-14kg/L
• Premature thelarche before 2 yrs
• 20% had soy formulae
• Women had more menstrual bleeding if fed soy formula in infancy

Soy in the prevention of atopy

• Sinn J and Osborn D
• 2006 Cochrane Review
Soy in the prevention of atopy

Diagnosis and Management of CMPA in Breast-Fed Infants

Diagnosis and Management of CMPA in Formula Fed Infants
Soy vs Cow's milk: Eczema

Use of soy in the community

- Lactose intolerance (rare) √
- Post infectious Lactose intolerance √
- CMP: trial if >6/12
- Reflux: x
- Colic: x
- Galactosemia: √
- Prevention of allergy: x

Cow’s milk allergy

- IF CM allergic (2% of population)
  - Antigen: casein, lactalbumin, and lactoglobulin
- Soy was discontinued in 47% cases
  - 53% in infants < 6 months and 35% in > 1yr
- Those with CMP allergy have a
  - 10-35% chance of allergy to Soy and
  - 2.2% to EHF

Iron deficiency  Sensitisation of Milk allergen

Milk allergen B lactoglobulin belongs to Lipocalins
And accommodate Iron complexes
If the CMP is unbound then it activates TH2
And IgE Ab develop against CMP
The Child then becomes sensitise to CMP

B lactoglobulin is an allergen when there is Fe deficiency
Goats milk

- Lower lactose 4.1 vs 4.7% cow milk vs BM 6.9%
- More protein 3.4 vs 3.2%
- More omega 3 25% more
- MCT 46% more vs CM
- Casein 2.6 vs CM 2.4%
- Cysteine 53% more than CM: use to protect GUT, antioxidant
  - Pasteurize the effect is null as a protein to convert to Glutathione.

Table 2. Average composition of basic nutrients in goat, sheep, cow and human milk

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Goat</th>
<th>Sheep</th>
<th>Cow</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (%)</td>
<td>3.8</td>
<td>7.9</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Solids - non-fat (%)</td>
<td>8.9</td>
<td>12.0</td>
<td>9.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Lactose (%)</td>
<td>4.1</td>
<td>4.9</td>
<td>4.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>3.4</td>
<td>6.2</td>
<td>3.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Casein (%)</td>
<td>2.6</td>
<td>4.2</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin, globulin (%)</td>
<td>0.6</td>
<td>1.0</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Non-protein N (%)</td>
<td>0.4</td>
<td>0.8</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Ash (%)</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Calories/100 ml</td>
<td>70</td>
<td>105</td>
<td>69</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 4. Average amino acid composition (g/l00 g milk) in proteins of goat and cow milk

<table>
<thead>
<tr>
<th>Essential Amino Acids</th>
<th>Goat</th>
<th>Cow</th>
<th>Difference (%) for goat milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan</td>
<td>0.044</td>
<td>0.046</td>
<td>+4</td>
</tr>
<tr>
<td>Threonine</td>
<td>0.163</td>
<td>0.149</td>
<td>+9</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>0.207</td>
<td>0.199</td>
<td>+4</td>
</tr>
<tr>
<td>Leucine</td>
<td>0.314</td>
<td>0.322</td>
<td>+4</td>
</tr>
<tr>
<td>Lysine</td>
<td>0.290</td>
<td>0.261</td>
<td>+11</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.080</td>
<td>0.083</td>
<td>+3</td>
</tr>
<tr>
<td>Cystine</td>
<td>0.046</td>
<td>0.030</td>
<td>+53</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>0.155</td>
<td>0.159</td>
<td>+4</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>0.179</td>
<td>0.159</td>
<td>+13</td>
</tr>
<tr>
<td>Valine</td>
<td>0.240</td>
<td>0.220</td>
<td>+9</td>
</tr>
</tbody>
</table>

Immediate allergic reactions

- IgE sensitisation
- 11-28% of anaphylactic reactions are due to CMA
- 11% fatal are CMA
- Cows milk protein allergy may manifest erythema, angioedema, urticaria or vomiting.
- Symptoms develop within minutes to 2 hrs
- Adrenaline Pens: Generic EpiPen off patent 2013
- Current sales 600mil for Antares, in 2015 it expect sales of 1.3bil
- Indicated especially those who has asthma, teenagers and nut allergies
**Atopic eczema**
- Associated with high levels of IgE to
  - milk, egg and peanut
- Egg is the most frequently involved allergen, followed by cows milk protein.
- IgE antibodies have been implicated in most cases of cows milk protein-induced eczema, about 10% of cases are not IgE associated.
- Sleep disturbances
- For the severe eczema 35% would benefit from food elimination

**CM protein induced enteropathy**
- Not IgE
- Diarrhoea
- Vomiting
- 80% respond to EHF
- Often allergic to soy, chicken, rice and fish
- Mx: mother avoid CMP. Egg?, Nuts?

**Gastro-oesophageal reflux disease (GORD)**
- Not IgE
- 40% reach specialist have CMPA
- Intestinal biopsy commonly shows partial villous atrophy.
- H2 blockers changes gut flora
- Aggravate the problem
- May cause more food allergies

**Severe irritability (colic)**
- Non IgE
- Persistent crying is a common problem that may affect about a third of young infants
  - gradually abates by 4 months of age
- Systematic review
  - Hypoallergic formula reduce colic
  - No role of soy in the prevention or management of infantile colic or regurgitation

**Constipation**
- Non IgE
- At tertiary referral level
- 70% of chronic constipation can be due to CMA
Size of the molecule

- Allergen 10000-70000 daltons
- Intact Soy 28000 daltons
- Partial hydrolysed 1100-10000 daltons
- Extensive hydrolysed < 1500
- Can be Allergenic if >1300 daltons
- Amino acid < 1000 daltons

Resolution of CMA

Delayed reaction vs immediate
- 2yr 64%: 31%  3yr 92%: 53%  4yr 96%: 63%
- Over estimation due to delay reintroduction
- Persistency:
  - infants reacting to <10 mL of milk
- Persistency:
  - larger wheal size on SPT, are at increased risk for persistence.

Decreasing IgE and Increase IgG4

Early recovery of CMPA
- 23 Children CMA and 6 controls follow to 9yrs
  - Those who recover from CMA
    - IgE binding decreases and IgG4 increase binding
    - This shows IgG4 induces tolerance by blocking the binding of specific IgE binding sites.
  - Future immunotherapy
  - Savilahti E, Sampson H JACI 2010

Immunotherapy

- No licensed immunotherapy products are available for the treatment of food allergy.
- Investigators are pursuing
  - via several different routes
    - oral, sublingual, and epicutaneous.

Cow milk allergy

- If SPT is positive to CM protein
- Then we offer gradual oral desensitisation
- Tablets made with increasing amounts
- If on Elemental formula can starting taking daily extensive hydrolysed formula tablets with a dalton size of 1500
- Take daily till develop symptoms
- This is the dose to commence desensitisation.
- Using gradual dalton size incrementation 2000, 3000, 4000, 20000
**Patterns of response to food OIT**

- **Allergy**
- **Failure to desensitize**
- **Partial desensitization**
- **Desensitization**
- **Tolerance**

**SLIT**

- Allergy drops
- Lower rate of severe reactions
- Weak strength may take 4-5 years to desensitize

**SCIT**

- SCIT: high rates of adverse events, particularly systemic reactions during the build-up phase,
- Including one fatality that occurred when a subject received an injection of peanut SCIT
- Those who complete the regimen, ~50% experience some degree of desensitization

**EPIT**

- In EPIT via patch
- Present antigen to dendritic cells, which are thought to induce pathways of the immune system.
- Used in milk allergy
- So far not successful in inducing desensitization to milk
- Studies using EPIT to treat other food allergies (e.g., peanut) are ongoing.

**CMA desensitisation**

- SPT > 3mm Sample size 20
- 1.5yr to 11 yr
- 55% allergic to other foods
- During challenge 60% had anaphylaxis and 30% had skin rash
- Increase IgG4 and decrease IgE decrease IL13

**Adjuvant**

- Prebiotics
- Probiotics
- Traditional Chinese medicine
- Omalizumab improves OIT for CMA
- SCIT Peanut absorbed with aluminium hydroxide safer then without
- Polyphenols, flavonoids, resveratrol,
**Cochrane Review HA: Primary Prevention**

Formulas containing hydrolyzed proteins for prevention of allergy and food sensitivity in infants (Review)

**CMA: PH Whey vs CMF**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>HR (95% CI)</th>
<th>Test for overall effect</th>
</tr>
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**Probiotic versus no probiotic:**

*Infant eczema: 13 trials, 1911 infants*

Heterogeneity: P = 0.37, I² = 8%
Test for overall effect:

P = 0.001  RR 0.79, 95%CI 0.68, 0.91

**Cases 1: Unsettle baby**

- 8 week old
- Crying, very unsettled
- Breast fed

**Case 2: Eczema**

- Severe eczema over the body
- 2 months of age
- Breast fed

**Case 3: Crying, possetting**

- 2 months of age
- Bottle feeding
Case 4: Blood in stools

- 4 week old
- Breast fed

Summary

- Many faces of cow's milk allergy
- Diagnosis: Exclusion
- Treatment: used Hydrolysed formula
- Immunotherapy: slow increase in size of molecule
- Resolution: time but increase with some exposure rather then none.

Take Home message

- Cow milk allergy: Ig E mediated
  - Potential Anaphylaxis
- Cow milk intolerance: Non IgE
  - Eczema
  - Blood in stools
  - Irritability
- Lactose intolerance: lack of lactase associated with diarrhoea and irritability
- Cow's milk protein is hydrolysed to decrease allergenicity which works for Allergy and intolerance.

The Paediatric Centre, St Leonards

OUR SERVICES

- Paediatric Allergy: Allergy testing and Immunotherapy
- Neonatologist
- Paediatric Nephrologist: Dr Fiona Mackie
- Allied Health
  - Clinical Psychologist, Occupational therapist, Physiotherapist, Speech therapist, Dietician,
- Any practical advice on your patient care please email or telephone:
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  - www.thepaediatriccentre.com.au