Zonulin as a marker of increased intestinal permeability in newborns suffering from viral infection of gastrointestinal tract

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The discovery of zonula occludens toxin (Zot) has shed light on the intricate mechanisms involved in the modulation of the intestinal paracellular pathway

Enterotoxin elaborated by Vibrio cholerae that affects TJ competency

Modulation defined as rapid, reversible and reproducible

Gut to play a pivotal role in the development of the systemic inflammatory response

ZONULIN (ZO) - 47 kDa protein - Pre - Haptoglobin 2
eukaryotic counterpart of the Vibrio cholerae zonula occludens toxin
**IDEA**

*Zonulin* - One of proteins associated with TJ - guanylate kinase like proteins ZO-1, ZO-2, ZO-3 with integral membrane proteins occludin and claudin (Fink MP, Tsukita S, Furuse M).

- Increases intestinal permeability
- Involved in intestinal innate immunity
- Unregulated in autoimmune diseases and immune mediated diseases (CD, MS, RA)
- Respiratory system - asthma (Blaisdell C, Fasano A)
- Nervous system diseases - association between schizophrenia and polymorphism (SNPs) related to HP gene (Arrieta et al., Turner R)
- Inflammation CD (Arrieta et al., BD (Turner R))
- Significantly higher plasma concentration of zonulin were found in sepsis (Klaus D A, et al, 2012)

**Question?**

What are the intestinal luminal stimuli that trigger zonulin release?

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**GI Rotavirus Infection**

*Rotavirus* - recognised in 1973, belongs to Reoviridae family

- Worldwide Rotavirus is estimated to cause more than 111 million cases per annum in children under 5 years of age
- Approximately 500,000 deaths per annum
- Infants younger than 3 months of age are said to be relatively protected
  - Transplacental antibodies
  - BM enteral feedings
- Moderate infection can lead to severe complications by influencing intestinal permeability

- Bacterial translocation
- Intestinal necrosis
- Sepsis

**Zonulin Estimation in GI Rotavirus Infection**

**Why?**

Serum proteins have the potential to be used as diagnostic and prognostic indicators for intestine injury.

- **Early Detection - Crucial**
  - **ZO** - a promising marker of intestinal permeability loss
  - **ZO** function by:
    - Genetic predisposition
    - Miscommunication between innate and adaptive immunity
    - Exposure to environmental triggers

- Emerging role of the gut barrier and microbiome in small bowel functional diseases
- Particular interest in the regulation of antigen trafficking by the zonulin pathway and its alteration by intestinal mucosa - microbiota
- GI rotavirus infection as triggering factor of zonulin release by altering and disintegrating the structure of TJ, therefore possible intestine injury and higher permeability status
Neonates (N=16) diagnosed with rotavirus infection confirmed by immunologic test
- median GA 38 wks
- median age 24th day of life

Serum ZONULIN was measured using ELISA test
ZO concentration compared with values evaluated in 14 terms apparently healthy neonates (no symptoms of infection

Routine laboratory evaluation was performed in all patients including:
- CBC with smear
- inflammatory markers (CRP, PCT)

RESULTS

<table>
<thead>
<tr>
<th>Parameter^</th>
<th>Study</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>ZO [mg/ml]</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>CRP [mg/dl]</td>
<td>0.7 (0.2-2.1)</td>
<td>0.2 (0.2-1.6)</td>
</tr>
<tr>
<td>PCT [mg/ml]</td>
<td>0.1 (0.1-0.3)</td>
<td>0.1 (0.1-1.1)</td>
</tr>
<tr>
<td>WBC</td>
<td>10.8x10^9</td>
<td>11.7x10^9</td>
</tr>
<tr>
<td>PLT</td>
<td>386x10^9</td>
<td>277x10^9</td>
</tr>
</tbody>
</table>

There was no statistically significant correlation between ZONULIN concentration and parameters of inflammatory status

Median values of CRP, PCT, leucocytes and platelets did not differ between the study group and controls

In all patients the course of rotavirus infection was uneventful

CONCLUSIONS

Significantly higher concentration of ZONULIN are found in neonates suffering from rotavirus infection

Higher concentration of ZONULIN may indicate higher permeability status of the intestine

Further observations are needed to reveal if serum ZONULIN value may correlate with the occurrence of intestinal complications even if inflammatory markers remain low
WHAT IS THE POTENTIAL OF THE IDEA?

SHORT TERM CONSEQUENCES
- Sepsis Prevention
- Enteral Feeding Tolerance
- Marker of Bacterial Translocation
- Inflammation Prevention
- Optimal Gut Microbiota

LONG TERM CONSEQUENCES
- Growth
- Immunocompetence
- Psychomotor Function

Zonulin genotyping to be correlated with the risk and severity of immune-mediated diseases (Fasano A, Clin Gastroenterol Hepatol. 2012)

THANK YOU FOR YOUR ATTENTION