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Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) and its soluble in the plasma form (sTREM-1) as a diagnostic biomarker in neonatal sepsis

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Abstract: Neonatal sepsis, defined as sepsis occurring within the first 28 days of life, is associated with significant morbidity and mortality. It is undeniable that finding and appliance of biomarkers in clinical practice is of great importance, aiming at the early recognition of the impending clinical deterioration and the prompt and targeted therapeutic intervention. After systematic and thorough research of the limited relevant literature, we attempt to present a documented point-of-view on the diagnostic value of TREM-1 and its soluble form both in early and late onset neonatal sepsis.

Key words: sepsis, neonate, TREM-1, biomarker, specificity, sensitivity.

Introduction

The critical time limit between early and late onset neonatal sepsis (EONS and LONS, respectively) is the first 72 hours after birth. Incidence of EONS in the United States of America (USA) is 0.76–0.77 new cases per 1000 live births, with estimated mortality rate is 24.4% [1]. Prevalence of LONS is 0.44%, while mortality rate exceeds up to 9% [2]. Very low birth weight neonates are particularly vulnerable to sepsis. Prevalence

of EONS in this subgroup is 1.5–2%, while prevalence of LONS exceeds up to 21% in the same subgroup [3]. Prematurity, co-morbidities and prolonged hospitalization in Neonatal Intensive Care Units (NICU) are aggravating factors, as well [3].

A biomarker is considered as significant in clinical practice, when it can be used for the early recognition of a septic patient and the prediction of his/her course, constituting a useful diagnostic tool (based on its specificity and sensitivity) for the early and prompt therapeutic intervention [4].

Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) is a member of the immunoglobulin superfamily, expressed on the surface of neutrophils, monocytes and macrophages, mainly via Toll-like receptors (TLR) ligands [5]. It interfaces with DAP-12, a transmembrane protein with ITAM (immunoreceptor tyrosine-based activation motif). This interaction induces an intracellular signal cascade [6]. Proteins JAK-STAT, ERK, AKT and finally NF-κB are the main mediators of the activated intracellular pathways. TREM-1 also exerts a regulatory role on signaling pathways, induced by known pattern recognition receptors (PRRs) classes [7]. TREM-1 activation leads to the production of pro-inflammatory cytokines and chemokines, increased expression of costimulatory molecules, reduction of IL-10 levels, while it induces degranulation of the neutrophils and increase in their phagocytic activity [8]. Expression of TREM-1 gene is induced, with favorable effect on the inflammatory process. Alongside, enzymatic cleavage of TREM-1 by sheddase results in increased plasma levels of the soluble form of TREM-1 (sTREM-1) [9, 10].

According to Garofoli *et al.* [11], neonatal immune system, despite its immaturity, is equipped with TREM-1. The authors studied 99 neonates and concluded that: a) TREM-1 expression in monocytes' surface was comparable with those in adults, b) sTREM-1 levels in neonatal plasma were comparable with those in adults and c) TREM-1 expression in polymorphonuclear neutrophils' surface was significantly lower than those in adults. Duration of gestation, maternal age, birth weight, way of delivery, sex, intrauterine growth restriction and pre-labor rupture of the membranes do not correlate with the assessed parameters. However, a statistical significant correlation between TREM-1 monocyte expression and surfactant administration was noticed [11].

Qian *et al.* [12] estimated TREM-1 membrane expression and functionality in healthy term newborns, compared to that of healthy adults. Cord blood samples from 20 healthy term newborns and peripheral blood specimens from 20 healthy adults were collected. Comparing the leukocyte TREM-1 expression between newborns and adults, according to Flow Cytometry results, almost all monocytes in newborns expressed TREM-1, a finding that was consistent with that of healthy adults (97.1 ± 8.3 vs. 97.5 ± 7.4 respectively, $t = 0.16$, $p = 0.87$), whereas, 80% of polymorphonuclear cells in newborns expressed TREM-1, slightly lower than in adults (82.3 ± 7.1 vs. 98.6 ± 4.8 respectively, $t = 8.51$, $p < 0.001$). However, TREM-1 mRNA

levels appeared significantly lower in newborns compared to adults, implying a slight immaturity of TREM-1 system in newborns (1.16 ± 0.13 vs. 1.63 ± 0.24 respectively, t = 7.7, p <0.001). After exposing cord blood samples in E. Coli, researchers reported significantly higher sTREM-1 levels 24 hours later, compared to the unexposed control group (1.16 ± 0.13 vs. 1.63 ± 0.24 respectively, t = 7.7, p <0.001). Also, sTREM-1 was positively correlated with tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and interleukin-6 (IL-6) levels, suggesting a potential diagnostic role of sTREM-1 in diagnosis of neonatal sepsis p = 0.019, 0.022, 0.014 respectively) [12].

After systematic and comprehensive research of the limited relevant literature, we attempt to present a documented point-of-view on the diagnostic value of TREM-1 and its soluble form both in early and late onset neonatal sepsis.

TREM-1 in clinical practice

Arizaga-Ballesteros *et al.* [13] studied 71 neonates with LONS, 9 of whom progressed to septic shock and/or death. Of the 62 neonates in LONS-Non Shock group, 20 presented with plasma sTREM-1 values above the limit of detection (sTREM-1>LOD), with the corresponding number for LONS & Shock/Death group being 8 of the 9 neonates. sTREM-1 median and interquartile range (IQR) plasma value were 10 (10 to 70) pg/mL in the LONS-Non Shock group and 567 (260 to 649) pg/mL in the LONS & Shock/Death group. ROC curve analysis revealed that the cut off value of sTREM-1 at 300 pg/mL could be considered as predictive of septic shock or death with 78% sensitivity and 97% specificity (AUC: 0.884, p <0.0001) [13].

Adly *et al.* [14] studied 112 newborns with sepsis (63 with positive blood culture, 32 of whom were preterm, and 49 with negative blood culture, 24 of whom were preterm) compared to 40 healthy newborns (control group), 18 of whom were preterm. They estimated sTREM-1 levels both at patient's admission and 48 hours after initiation of the antibiotic treatment. Baseline levels of the measured biomarker were significantly higher in septic neonates compared to control group (p <0.001). In addition, sTREM-1 levels were: a) similar in the two groups of septic neonates (p >0.05), b) higher in preterm than in full-term septic neonates, c) higher in neonates suffering from EONS than in neonates with LONS (p <0.001) and d) significantly lower 48 hours after initiation of antibiotic treatment than in patient's admission, both in positive and negative blood culture groups (p <0.001). No correlation of the measured levels of sTREM-1 with the isolated from the blood culture pathogen was observed [14].

Stein *et al.* [15] compared the diagnostic value of sTREM-1, C-reactive protein (CRP) and procalcitonin (PCT) as for the early and prompt recognition of neonates and infants aged less than 3 months with severe bacterial infection (SBI). Their sample consisted of 112 patients, 19 of whom suffered from SBI and 93 of whom had

a negative blood culture. Regarding the discussed biomarker, the sensitivity was 82%, the specificity was 48% and the AUC 0.61. sTREM-1 overall exhibits higher sensitivity (82% vs. 45% of CRP and 55% of PCT), but significantly lower specificity (48% vs. 82% of CRP and 75% of PCT) [15].

In their prospective clinical study, Sarafidis *et al.* [16] evaluated the diagnostic value of sTREM-1 in comparison with that of IL-6 in the early recognition of neonates, preterm or full-term, suffering from LONS. They divided their patients into two groups, group A (neonates with confirmed or suspected sepsis, n = 31) and group B (neonates without underlying infection, n = 21). Levels of both biomarkers were significantly higher in group A than in group B ($p = 0.004$ and $p < 0.0001$ for sTREM-1 and IL-6 respectively, AUC = 0.733 and 0.892 respectively). Despite the limitation of the small sample, it is noted that sTREM-1 can be useful for identification of septic neonates, but is not advantageous, when compared to IL-6 [16].

Saldir *et al.* [2] published the results of their study including 50 neonates, 20 non-septic and 30 septic, through which they attempted to compare the diagnostic accuracy of sTREM-1 and endocan in LONS to that of conventional biomarkers in sepsis, IL-6 and immature /total neutrophil ratio (I/T ratio). Researchers reported significantly higher sTREM-1, IL-6, endocan and I/T ratio levels in septic neonates compared to non-septic neonates. All biomarkers yielded significant AUCs with respect to early diagnosis of neonatal sepsis, with sTREM-1 and IL-6 performing best to differentiate septic from non-septic neonates. The AUC was 0.97 ($p < 0.001$) for sTREM-1 and 0.96 for IL-6 ($p < 0.001$), whereas the AUC was 0.80 for endocan ($p < 0.001$) and 0.90 for I/T ratio ($p < 0.001$). The suggested cut-off points were 7 ng/mL for IL-6 and 450 pg/mL for sTREM-1 and these settings resulted in 93.3% sensitivity and 95% specificity for IL-6 and 93.3% sensitivity and 90% specificity for sTREM-1. Researchers concluded that sTREM-1 had better diagnostic accuracy when compared with endocan and I/T ratio, but lower than IL-6. Finally, the authors believe that sTREM-1 could also be used as a prognostic marker, after noticing that sTREM-1 levels significantly decreased 48–72 hours after initiation of the targeted antibiotic treatment [2].

Conclusions

- sTREM-1 levels exhibit a positive correlation with the progression and the severity of the septic syndrome, and the response to the targeted therapeutic intervention, as well.
- sTREM-1 levels exhibit comparable diagnostic value with those of conventional biomarkers in sepsis, such as CRP and PCT, but sTREM-1 is inferior to other recently developed biomarkers, such as IL-6.

- Combination of sTREM-1 with other biomarkers, in a multi-marker panel, may become the reference diagnostic test in sepsis.
- Further relevant research data are expected towards the consolidation of sTREM-1 as a diagnostic biomarker in clinical practice of sepsis.

Conflict of interest

None declared.

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