# Progranulin in diagnosis of early onset neonatal sepsis. Is it reliable?

**Rahf.Sh.Mohamed[1], Omayma.M.Abd El hay[1], Soha.A.El-Gendy[1]and Rana.A.Khashaba[2]**
[1]Pediatrics Dept., Faculty of Medicine, Banha University
[2]Clinical Pathology Dept., Faculty of Medicine, Banha University
**E-mail:** rahfsherif92@gmail.com

**Abstract**

**Background:** Neonatal sepsis is a serious health issue. Proper diagnosis and treatment can help these neonates have better outcomes. **Objective:** Progranulin was evaluated for its value in early-onset neonatal sepsis (EONS). **Methods:** The neonates in this study were hospitalized in the Neonatal Intensive Care Unit within the first seven days of life. The septic group contained 10 neonates, and the control group included 10 healthy neonates. All neonates had thorough clinical evaluations and lab testing. **Results:** Septic neonates had more risk factors as birth trauma. Clinical signs were variable including respiratory distress and neurological signs. The total leucocytic count was higher in septic neonates as well as progranulin. **Conclusion:** Progranulin was elevated in EONS and may be helpful for diagnosis.

**Keywords :** Neonate, Sepsis, Risk factors, Complications.

## 1. Introduction

The pathophysiological consequences of a severe bacterial infection during the first month of life might lead to a clinical illness known as neonatal sepsis. Syphilis is characterised by a cluster of symptoms brought on by microorganisms or their harmful byproducts in the bloodstream, as opposed to bacteremia, which is the presence of bacteria in the blood. Based on the symptoms the patient has, bacteremia might escalate to septicemia (1). But there are cases when bacteremia isn't present—for example, culture-negative sepsis in pyelonephritis or endotoxemia pneumonia (2).

The principal pathogen involved in neonatal sepsis has tended to change with time. The agents associated with primary sepsis are usually the vaginal flora. Most centers report group B Streptococci (GBS) as the most common followed by Gram-negative enteric organisms, especially Escherichia Coli (E coli), other pathogens include Listeria Monocytogenes, Staphylococcus, other Streptococci, anaerobes and Haemophilus Influenza. The flora causing nosocomial sepsis varies in each nursery, Staphylococci (especially Staphylococcus Epidermidis), Gram-negative rods (including Pseudomonas, Klebsiella Serratia, and Proteus), and fungal organisms predominate (3).

There is no classic presentation of neonatal sepsis. Any clinical sign has an extensive differential diagnosis (4). Symptoms and signs of sepsis include respiratory distress or apnea, fever or hypothermia, vomiting, seizures, poor perfusion, shock, petechiae or purpura, unexplained jaundice, or most important [not doing well] (5).

Even though normal total leucocytic counts (TLCs) may be seen in up to half of the cases with culture-proven sepsis, platelet counts are less sensitive for identifying sepsis than TLCs and ratios. Stress after childbirth may cause aberrant TLC in healthy infants as well (6).

Meningitis in neonatal sepsis is clinically indistinguishable from bacteremia without a focus and 10% - 38% of neonates with meningitis have negative blood culture, so lumbar puncture is necessary to determine the presence or absence of meningeal involvement (7).

Many acute phase proteins including haptoglobin, alpha 1 antitrypsin, fibronectin, lactoferrin, neopterin and orosomucoid, have been evaluated in relation to neonatal sepsis. Calprotectin is a major product of the innate immune cells that was found to be of benefit for diagnosis of neonatal sepsis with sensitivity 89% and specificity 96% (8).

There is strong evidence that clean delivery practices and hand washing during delivery reduces rates of neonatal sepsis in both home and health facility settings. The reasons for lack of successful scale up of hand washing interventions into policy, programs, and behaviour change are less clear (9).

Neonatal sepsis early antimicrobial regimens should still include ampicillin and gentamicin. These broad-spectrum antibiotic regimens work synergistically against GBS and Listeria monocytogenes, the two most prevalent causes of newborn sepsis (GBS and E. coli account for over 70% of cases) (10).

## 2. Subjects & Methods:

This was a prospective study conducted between January 2022 and June 2022, at the neonatal intensive care unit, on neonates admitted during the first week (first seven days) of life. The study comprised 20 neonates. Neonates were divided into two groups; the septic group contained 10 neonates, and the control group included 10 healthy neonates. Septic neonates had signs of neonatal sepsis.

All neonates were subjected to the following:

**A. Full history taking: -**

✓ Antenatal history: Include illness, infections, drugs, radiation, vaccination, health and nutrition of mother during pregnancy.

✓ Natal history: Include type of delivery, presentation, rupture of membrane time,

gestational age, place of delivery, conducted by sterilization, labour time, sedation during labour, and complications.

✓ Post-natal history: First cry, birth weight, injury, fever, rash, basic problems, convulsions, cyanosis, any procedures, or drugs.

**B.  Examination: -**

- Vital signs: Pulse, temperature, respiratory rate.
- Estimation of gestational age: Skin texture, lanugo hair, creases, breast, eye, ear and genitalia.
- Neurological examination: Muscle tone, and reflexes including moro, grasp, suckling and rooting.
- Physical examination: Capillary refill, measurements, general, head and neck, chest, heart, abdomen, extremities.

**C- Laboratory Investigations:**
Blood test for CBC and progranulin.

**3.Results:**

Birth trauma was a significant risk factor for EONS. Regarding anthropometric measures there was no significant difference between the two groups regarding weight, length and head circumference **(Table 1).** Moreover, there was no significant difference between the two groups regarding heart rate, respiratory rate & temperature **(Table 2).**

Clinical signs of septic group including apnea, bradycardia, hepatomegaly, hypoglycaemia and neurological signs were significantly higher at time of diagnosis compared to the control group, while signs as hypotonia and jaundice were not significantly different between the two groups **(Table 3).**

**Table (1)** Comparison between the study groups regarding anthropometric measures

|  | Septic group | | Control group | | t | p-value |
|---|---|---|---|---|---|---|
| **Anthropometric measures.** | Mean | ± SD | Mean | ± SD | | |
| Weight | 3.13 | 0.46 | 3.15 | 0.30 | 0.2 | 0.8 |
| Length | 43.93 | 5.95 | 44.35 | 4.87 | 0.4 | 0.7 |
| Head circummference | 34.6 | 3.09 | 34.8 | 3.18 | 0.248 | 0.543 |

**Table (2)** Comparison between the study groups regarding vital signs at time of admission.

|  | Septic group | | Control group | | t | p-value |
|---|---|---|---|---|---|---|
| **vital signs** | Mean | ± SD | Mean | ± SD | | |
| Heart rate | 133.03 | 28.02 | 137.95 | 7.23 | 1.1 | 0.3 |
| Respiratory rate | 56.9 | 8.73 | 54.93 | 15.25 | 0.71 | 0.48 |
| Temperature | 36.98 | 0.32 | 36.97 | 0.27 | 4.42 | 0.06 |

**Table (3)** Comparison between the study group regarding neonatal clinical signs.

| **Clinical Examination.** | Septic group | | Control group | | $X^2$/FET | p-value |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| General signs | | | | | | |
| Hypothermia | 5 | 50 | 0 | 0 | 28.5 | <0.001* |
| Poor suckling | 5 | 50 | 0 | 0 | 28.5 | <0.001* |
| Hypoactivity | 4 | 40 | 0 | 0 | 23.2 | <0.001* |
| Jaundice | 7 | 70 | 5 | 50 | 0.14 | >0.99 |
| Respiratory signs | | | | | | |
| Respiratory distress | 6 | 60 | 2 | 20 | 28.6 | <0.001* |
| Apnea | 2 | 20 | 1 | 10 | 8.5 | 0.003* |
| Cardiovascular signs | | | | | | |
| Tachycardia | 2 | 20 | 0 | 0 | 6.8 | 0.003* |
| Bradycardia | 3 | 30 | 0 | 0 | 12.8 | <0.001* |
| Hypotension | 3 | 30 | 0 | 0 | 16.9 | <0.001* |
| Perfusion changes | 5 | 50 | 0 | 0 | 23.2 | <0.001* |
| Gastrointestinal signs | | | | | | |
| Diarrhoea | 2 | 20 | 0 | 0 | 12.8 | <0.001* |
| Abdominal distension | 6 | 60 | 0 | 0 | 34.3 | <0.001* |
| Hepatomegaly | 2 | 20 | 0 | 0 | 8.1 | 0.001* |
| Hypoglycaemia | 4 | 40 | 0 | 0 | 23.2 | <0.001* |

| Central nervous system signs | | | | | | |
|---|---|---|---|---|---|---|
| Jitteriness | 4 | 40 | 0 | 0 | 20 | <0.001* |
| Seizure | 2 | 20 | 0 | 0 | 8.1 | 0.001* |
| Hypotonia | 1 | 10 | 0 | 0 | 3.4 | 0.06 |
| Renal signs | | | | | | |
| Oliguria | 2 | 20 | 0 | 0 | 12.8 | <0.001* |

In the present study, the septic group had statistically higher TLC and had a statistical lower levels of platelets and haemoglobin. Progranulin was slightly higher in septic neonates than the control group.

## 4.Discussion

Birth trauma was a significant risk factor. This has been explained before as procedures disturbing the integrity of uterine contents as amniocentesis, cervical cerclage, transcervical chorionic villus sampling or percutaneous blood sampling permit entry of vaginal organisms to the skin causing amnionitis and secondary fetal infection (11).

Over the last half-century, there has been a shift in the infectious agents linked to newborn sepsis. Infectious newborns in the US were most often exposed to Staph aureus and Escherichia coli in the 1950s. As the leading gram-positive bacteria responsible for early-onset sepsis, GBS surpassed Staph. aureus in prevalence throughout the subsequent decades (12).

Our study revealed that the septic group had a statistically higher frequency of hypothermia (50% , p<0.001), poor suckling (50% , p<0.001), hypoactivity (40% , p<0.001), apnea (20% , p=0.003), respiratory distress (60% , p<0.001), bradycardia (30% , p=0.003), tachycardia (20% , p=0.003), hypotension (30% vs, p<0.001), neurological signs {seizure (20% , p<0.001), jitteriness (40% , p<0.001), hypotonia (10% , p=0.06)}, poor suckling (50% , p<0.001), abdominal distension (60% , p<0.001), diarrhoea (20 % , p<0.001), hepatomegaly (20 % , p<0.001), while there was no significant difference regarding jaundice (p=0.99).

This jibes with other research that found hypothermia, delirium, poor eating, bewilderment, and confusion to be symptoms of sepsis. Babies with early-onset sepsis and negative blood cultures seldom show elevated temperatures. Term and preterm infants may be diagnosed with bacterial infections based on temperature signs. Unspecific symptoms of sepsis include a racing heart, shivering, chills, rash, hot skin, hyperventilation, moderate respiratory distress at a rate of >60-70/min with little recession, and hyperventilation. Premature babies often have cyanosis and apnea, which might indicate sepsis (13).

Asymptomatic newborns make up over 30% of cases of neonatal meningitis, and the symptoms are sometimes vague and difficult to diagnose. Symptoms of central nervous system infections (CNS infections) appear as newborn sepsis, which includes unstable body temperature, respiratory distress, jaundice, and apnea. Meningitis is more clearly indicated by symptoms involving the central nervous system (CNS), such as fatigue, seizures (especially focal ones), vomiting, and irritability. About 25% of cases have a full or bulging fontanelle, whereas only 15% have nuchal stiffness. Additionally, there could be anomalies with the cranial nerves (14).

Compared to the healthy control group, those with septic shock had significantly lower levels of haemoglobin and platelets and a greater TLC. A healthy newborn's platelet count in the first ten days of life is usually more than 100,000/mm3. As a result of exposure to microbial cellular products, newborn sepsis may cause thrombocytopenia with counts below 100,000/mm3. Platelets cluster and stick to these products, which destroys them. Thrombocytopenia, a complication of sepsis, typically persists for one week but may persist for up to three weeks. Because freshly generated platelets only show up in 10–60% of neonates with sepsis (15).

Previous reports have shown that progranulin is associated positively with meningitis, pneumonia, and mortality; the present investigation confirmed this finding in septic newborns. Research into progranulin's intracellular location has shown that it is located in the secretory vesicles of active leukocytes, which might indicate that it is a secreted growth factor. One possible role for secreted progranulin in tissue healing is its ability to stimulate mitogenesis in epithelial cells (16). After injury, progranulin is up-regulated in fibroblasts and endothelial cells, where it is typically not expressed. Additionally, it is up-regulated in keratinocytes, macrophages, and neutrophils that are linked to the injured tissue. The released protein progranulin stimulates neovascularization of injured tissue and speeds up neutrophil and macrophage activity, but it has little effect on in vivo healing rates (17).

## 5.Conclusion:

Septic neonates had more risk factors, clinical signs and complications than control. Progranulin was higher in septic neonates and correlated with disease severity.

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