

Serum Copeptin Level as a Predictor of Outcome in Pneumonia

This cross-sectional study included 41 children (age 2 mo-12 y) with pneumonia and 40 healthy controls. Assay of serum copeptin was done using ELISA. Median serum copeptin levels were significantly higher ($P=0.03$) in children with pneumonia, and in those who died ($P=0.04$). We conclude that serum copeptin levels seem to be associated with poor outcome in pneumonia.

Keywords: Copeptin, Pneumonia, Prognosis.

Pneumonia is one of the important causes of morbidity and mortality in under-five children [1]. Vasopressin is derived from a larger precursor peptide (pre-provasopressin), and is released together with copeptin in equimolar ratio to vasopressin mirroring its levels, and is more stable to measure in the circulation [2]. An increment in copeptin level with the severity of sepsis, and it being an independent predictor of mortality in pneumonia has been reported in adults [3,4]. This study aimed to assess the diagnostic and prognostic significance of copeptin levels in pediatric pneumonia.

This case-control study was conducted at Faculty of Medicine, Cairo University, Egypt, from January 2013 to December 2013. It included 41 children (2 months to 12 years) with a diagnosis of community-acquired pneumonia (WHO definition of pneumonia and having X-ray findings), or ventilator-associated pneumonia (pneumonia occurring more than 48 hours after patients have been intubated and received mechanical ventilation with Clinical Pulmonary Infections Score (CPIS) [5] above six). Patients who had been hospitalized and treated with antibiotics for ≥ 48 hours, and those having dehydration, immunodeficiency or malignancy, were excluded. Forty healthy matched children were included as controls. Serum copeptin was assayed by a commercial ELISA kit (sensitivity 1.0 pg/mL). A written informed consent was obtained from parents before enrolment. Statistical analysis was performed using Minitab 17. Receiver operating characteristic (ROC) curve was plotted to estimate predictive capability of copeptin for disease. P value < 0.05 was considered statistically significant.

The study included 29 children with community acquired pneumonia (CAP) and 12 children with ventilator-associated pneumonia (VAP). Thirteen children

with pneumonia died. Median copeptin levels were significantly higher in patients compared to controls (31.2 vs. 25.3 pg/mL; $P=0.03$). Median copeptin levels were significantly higher in children who died as compared to survivors (89.5 vs. 28.1 pg/mL; $P=0.04$). There were no significant differences in median copeptin levels between CAP and VAP patients (31.2 vs. 30.6 pg/mL; $P=0.81$). On logistic regression analysis, mechanical ventilation was the only independent variable associated with high odds of mortality (OR 10.0; 95% CI 2.1, 47.0). High (> 56 pg/mL) copeptin level was not an independent predictor of mortality (OR 2.4; 95% CI 0.6, 9.4). ROC curve (**Fig. 1**) showed area under curve (AUC) of 0.62, with copeptin cut-off point of 56 pg/mL having sensitivity and specificity of 39% and 85%, respectively, for diagnosis of pneumonia.

The present study detected elevated copeptin in children with pneumonia, with significantly higher levels in non-survivors compared to survivors. However, high copeptin level was not an independent predictor for mortality. Copeptin showed low sensitivity but high specificity for diagnosis of pneumonia.

Our findings are comparable to previously published literature reporting serum concentrations of copeptin to be significantly higher in patients with CAP or VAP, and their complications [6-9]. The limitations of present study are

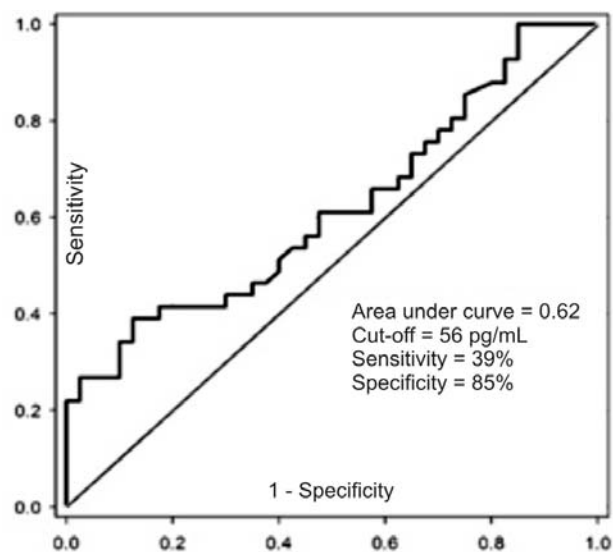


FIG. 1 Receiver operating characteristics (ROC) of serum copeptin levels for diagnosis of pneumonia.

small sample size and lack of work-up for viral and bacterial pneumonias. We conclude that circulating levels of copeptin are significantly increased in children with pneumonia, and are higher in children dying of the disease. Copeptin levels might predict unfavourable outcome in pediatric pneumonia.

Contributors: All authors have contributed, designed and approved the study.

Funding: None; *Competing interest:* None stated.

MOHAMMED ABDEL-FATTAH, *BASSANT MELIGY,
#RIHAM EL-SAYED AND YOSRA A EL-NAGA

*From Departments of Pediatrics and #Clinical and Chemical Pathology; Faculty of Medicine, Cairo University, Egypt.
basantsalah2003@yahoo.com

REFERENCES

- Selvaraj K, Chinnakali P, Majumdar A, Krishnan IS. Acute respiratory infections among under-5 children in India: A situational analysis. *J Nat Sci Biol Med.* 2014;5:15-20.
- Katan M, Müller B, Christ-Crain M. Copeptin: A new and promising diagnostic and prognostic marker. *Crit Care.* 2008;12:1172.
- Seligman R, Papatotirius J, Morgenthaler NG, Meisner M, Teiceira PJ. Copeptin, a novel prognostic biomarker in ventilator-associated pneumonia. *Crit Care.* 2008;12:R11.
- Palmiere C, Augsburger M. Copeptin as a diagnostic biomarker for sepsis-related deaths. *Peptides.* 2014;59:75-8.
- Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med.* 2000;162:505-11.
- Zhao YF, Lin Y, Zhang WG. (Clinical significance of serum copeptin in patients with community-acquired pneumonia). *Zhonghua Jie He He Hu Xi Za Zhi.* 2009;32:911-4 (Chinese).
- Du JM, Sang G, Jiang CM, He XJ, Han Y. Relationship between plasma copeptin levels and complications of community-acquired pneumonia in preschool children. *Peptides.* 2013;45:61-5.
- Boeck L, Eggimann P, Smyrnios N, Pargger H, Thakkar N, Siegemund M, *et al.* The Sequential Organ Failure Assessment score and copeptin for predicting survival in ventilator-associated pneumonia. *J Crit Care.* 2012; 27:523.e1-9.
- Krüger S, Ewig S, Kunde J, Hanschmann A, Marre R, Suttorp N, *et al.* CAPNETZ Study Group. C-terminal provasopressin (copeptin) in patients with community-acquired pneumonia—influence of antibiotic pre-treatment: results from the German competence network CAPNETZ. *J Antimicrob Chemother.* 2009;64:159-62.

Screening for Thalassemia Carrier Status in Pregnancy and Pre-Natal Diagnosis

This hospital-based study reports the results of antenatal screening for thalassemia in pregnant women visiting a hospital in Jodhpur, Rajasthan, India. Eighty-eight (5.9%) of 1500 women screened for thalassemia had thalassemia trait. Twenty at-risk couples were identified and two fetuses were detected to be having thalassemia major.

Keywords: *Abortion, Pregnancy, Prenatal diagnosis.*

The most effective and feasible approach to reduce the incidence of thalassemia major is implementation of carrier screening program to test the mothers antenatally as early as 8-12 weeks of pregnancy, offering genetic counseling, prenatal diagnosis and selective termination of affected fetuses. This study was planned to determine the frequency of carrier status of thalassemia in pregnant females visiting our hospital to identify “at-risk” couples, and to prevent birth of new cases of thalassemia major.

This observational study was conducted over 18 months in Departments of Pediatrics, and Obstetrics and Gynecology, Umaid Hospital, Dr. Sampurnanand Medical College, Jodhpur, India. Pregnant women in first trimester and early second trimester (<16 weeks), who were willing for carrier screening, were screened by hematological indices after an informed consent. Detailed history to ascertain the ethnic descent, and any history of blood transfusion was obtained. Complete blood count was done on automated cell counter (Sysmex K-100) and hematological parameters were recorded for 1500 women. HbA₂ estimation was done in females with either of the following: (a) MCV <77 fL (b) MCH <27 pg, (c) Mentzer Index <13, (d) family history of thalassemia, (e) high risk ethnic groups – Punjabis, Sindhis, Gujaratis, Bohris and Malis, (f) history of blood transfusion, or (g) unexplained chronic anemia. Women who attended the antenatal clinics in late second trimester and third trimester or those who did not consent were excluded. HbA₂ estimation was performed using HPLC (High Performance Liquid Chromatography). HbA₂ >3.5% confirmed the diagnosis of β-thalassemia trait. Those with HbA₂ in the borderline range (3.3-3.4%) were screened for thalassemia mutations by ARMS-PCR (Amplification Refractory Mutation

System - Polymerase Chain Reaction). Chorionic villous sampling (CVS) was done if gestational age was <12 weeks and amniocentesis was preferred for cases detected in later weeks of pregnancy. ARMS-PCR was used for genetic analysis.

Out of 1500 pregnant women, 450 required HbA₂ estimation, and 88 (5.9%) were diagnosed as β -thalassemia trait. Mean (SD) age and gestational age of these women was 25.2 (4.2) y and 11.8 (1.4) wk, respectively. Forty-five (45%) had family history of thalassemia. Husbands of 80 of these women responded for screening and 20 proved to be thalassemia trait. Seventeen out of 20 at-risk couples agreed for prenatal diagnosis. Amniocentesis was done in thirteen and CVS in four pregnancies. Two fetuses were detected as having thalassemia major, and medical termination of pregnancy was done. Eleven fetuses were detected as having thalassemia trait and 4 without any β -globin chain abnormality. The mutations detected are depicted in **Table I**. Most common mutations were IVS 1-5 (G-C) > Fs8/9 β -globin > 619bpdel=fs41/42=codon 30G-C > codon β 8 > Cap+1 (A-C). Five most common mutations were present in 77% of alleles. No complication occurred in CVS/amniocentesis conducted.

TABLE I RESULTS OF MUTATION ANALYSIS IN THE STUDY CHILDREN (N=17)

Mutation	Mother	Father	Fetus
IVS 1-5 (G-C) heterozygous	6	6	6
Fs 8/9 β -Globin heterozygous	5	6	5
619 bp del β -Globin			
heterozygous	1	1	-
homozygous	-	-	1
Codon β -8 (-AA) heterozygous	1	1	1
Codon 30 G-C heterozygous	1	1	1
Fs 41/42 heterozygous	1	1	1
Cap+1(A-C) heterozygous	1	-	-
Compound heterozygous (Fs 8/9 and IVS 1-5(G-C))	-	-	1
No Mutation	1	1	1

The sample size of our study was small and three couples could not be persuaded for prenatal diagnosis despite repeated counseling. Colah, *et al.* [1] conducted prenatal diagnosis on only 15 out of 37 at-risk couples over a period of 7 years, and Xu, *et al.* [2] carried prenatal diagnosis in 11 out of 12 at-risk couples. Five common mutations were reported to be present in 89% thalassemia patients in an earlier study [3] from India. Saxena, *et al.* [3] reported abortion rate of 3.9% following prenatal diagnosis. Antenatal screening of pregnant females is the most feasible and effective method to reduce birth of children with thalassemia. Carrier screening for thalassemia and hemoglobinopathies should be offered and genetic counseling should be done to women at-risk of these disorders.

Contributors: VD: design of the study, analysis, drafting and final approval of the manuscript; PS: data acquisition, data analysis, revision of the manuscript for important intellectual content and final approval; RJ: data analysis, revision of the manuscript and final approval; MA: analysis of data, data acquisition, drafting of the manuscript and final approval; AK: analysis of data, data acquisition, drafting of the manuscript and final approval.

Funding: Marwar Thalassemia society, Rajasthan; *Competing interests:* None stated.

***VIDIT GUPTA, PRAMOD SHARMA, RAKESH JORA, MINHAS AMANDEEP AND ANJANI KUMAR**

*Department of Pediatrics,
Dr SN Medical College,
Jodhpur, Rajasthan, India.
vidit_gupta9@yahoo.co.in

REFERENCES

- Colah R, Surve R, Wadia M. Carrier screening for β -thalassemia during pregnancy in India: A 7-year evaluation. *Genet Test*. 2008;12:181-6.
- Xu X, Liao C, Liu Z, Huang Y, Zhang J, Li J, *et al.* Antenatal screening and fetal diagnosis of β -thalassemia in a Chinese population: prevalence of the β -thalassemia trait in the Guangzhou area of China. *Hum Genet*. 1996;98:199-202.
- Saxena R, Jain PK, Thomas E, Verma IC. Prenatal diagnosis of β -thalassemia: Experience in a developing country. *Prenat Diagn*. 1998;18:1-7.