

The Armenian SORT IT Course

Liver involvement in the process of acute respiratory infections in pediatric patients

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Abstract

Introduction: We aimed to investigate the prevalence of liver involvement in pediatric patients with ARI using both routine tests of hepatic panel, and ornithine carbamoyltransferase (OCT) to identify the most sensitive indicators of early hepatic injury.

Methodology: A prospective cohort study of 84 armenian children with ARI was conducted to evaluate the associated liver involvement. The diagnostic variables of interest were the signs of clinical disease severity, and enzymatic profile of the patients.

Results: Serum levels of OCT were increased in 94% of patients versus routine tests of hepatic panel (AST in 41.7%, ALT in 15.5%, etc). Variance analysis by severity groups showed the serum levels of OCT ($p < 0.001$), ammonia ($p < 0.001$), phospholipides ($p = 0.05$), glucose ($p = 0.01$), TNF- α ($p = 0.01$), IL-8 ($p < 0.001$), AST ($p < 0.001$), and ALP ($p < 0.001$) were associated with the severity of underlying disease. Moreover, regression analysis revealed the serum activity of OCT (p value < 0.001 , OR = 1.27) and ammonia (p value 0.002, OR = 1.1) significantly predict the severity of the disease.

Conclusions: Using more sensitive marker of liver damage can detect more cases of ARI with hepatic manifestations. For evaluation of the liver involvement we are suggesting the testing of serum OCT levels as a more sensitive and specific marker. Pediatric patients with ARI and with higher serum OCT levels have 27% more chance to experience increased disease severity, which can affect on liver state and prolong hospitalization time and cost.

Key words: Ornithine carbamoyltransferase (OCT); liver dysfunction; liver panel; noninvasive indicators of liver damage, acute respiratory infection (ARI).

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Introduction

Acute respiratory infections (ARI) are the most common cause of hospitalization in infants and young children. Recently, the problem of hepatic involvement in ARI was highlighted by several studies [1-6]. The liver is a sensitive organ and it can be affected in various diseases occurring either by direct invasion of pathogens or indirectly through internal toxins and cytokines activation mechanism. Liver involvement in various diseases without direct invasion of pathogen is defined as the secondary hepatic dysfunction or collateral damage of the liver [1,2]. Liver damage during ARI has been demonstrated in animal models, showing that virus replication is not the primary reason for hepatocellular injury. Production of cytokines (TNF- α , IL-6, IL-8, IL-10) results in hepatic oxidative stress leading to the hepatocyte injury [6,7]. Furthermore, the overproduction of cytokines can damage the liver [7,8]. The derivatives of lipid

peroxidation (LP), necrosis of hepatocytes, TNF- α , IL-6, IL-8 are all act as the activators for stellate cells which in turn stimulate the overproduction of connective tissue with the further development of fibrosis.

This study was carried out to assess the prevalence of liver involvement in pediatric patients with ARI using not only routine tests of hepatic panel, but also ornithine carbamoyltransferase (OCT) to identify the most sensitive indicator of early hepatic injury.

Methodology

Study design and setting

A prospective cohort study was conducted over a 5-months period (2009 November - 2010 April) at Muratsan Hospital Complex of Yerevan State Medical University after M. Heratsi, Republic of Armenia. 84 hospitalized children aged from 3 months to 16 years old with ARI were observed. Genders were

approximately equal: 50.4% boys and 49.6% girls. Half of them was diagnosed with community acquired pneumonia (CAP) and the other half - with acute bronchitis (AB). Children with preexisting liver diseases and history of drug taking were excluded to target only suspected secondary abnormalities in the liver. Blood samples were collected at admission before starting treatment. All patients received the accepted standard treatment of ARI afterwards.

Data were obtained from each patient in a predesigned data collection form, which included demographic information, time of disease onset, clinical manifestations, signs of toxic appearance and clinical disease severity.

Study Interventions

Study activities included evaluation of patients’ enzymatic profile, serum levels of some proinflammatory cytokines (TNF- α , IL-6, IL-8), free-radical oxidation parameters, ammonia, albumin, bilirubin and other standard procedures. All patients underwent abdominal ultrasound examination. The diagnostic variables of interest were the signs of toxic appearance and disease severity (dark circles under the eyes; skin dryness, paleness nausea and/or vomiting; rapid loss of energy and fatigue), hepatomegaly, serum transaminases activity, cholestasis (ALP, gamma glutamyl transferase (γ GT)), serum levels of OCT, hypoalbuminemia, indicators of dyslipidemia (phospholipids (PhL), β -lipoproteins), hypoglycemia, indicators of lipid peroxidation (LP), hypercytokinemia, hyperammonemia. The method used for estimation of OCT was based on the Soman’s method. The citrulline formed from ornithine and carbamoyl phosphate catalysed by OCT, is reacted with

diacetyl monoxime at low acidity [24]. Laboratory reference ranges are presented in Table 1.

For the purposes of this study individuals were placed in one of 3 main groups based on assessment of the severity levels of the underlying disease: mild (group 1), moderate (group 2), and severe (group 3). OCT activity was characterized as minimally (21.1-24 U/L), moderately (24.1-30.2 U/L), and significantly increased (> 30.2 U/L).

Statistical analysis

All variables for evaluation of liver dysfunction and severity of primary disease were included in statistical analysis. Descriptive analysis (Mean \pm SD for continuous variables and frequencies/proportion for categorical variables) were conducted for all variables. The means between groups divided by severity were compared using the analysis of variance (ANOVA) for parametric data and Kruskal Wallis for non-parametric data. The correlation between variables in groups and in the cohort were analyzed using Pearson’s and Spearman’s tests. All data was analyzed using SPSS 16.0.R software was used for generating graphs and validating SPSS data analysis reports.

Ethical considerations

Ethics approval was obtained from the Institutional Review Board of Yerevan State Medical University after M. Heratsi, RA. Study participation assent was obtained for each patient from a parent.

Results

Descriptive data

Descriptive characteristics of patients include signs of toxic appearance and clinical disease severity: dark circles under the eyes 62 (73.8%), skin dryness 37

Table 1. Reference ranges for laboratory values.

Chemistry variables	Normal range	Measurement unit
Lipid peroxides	3-4.5	g/L
Phospholipids	< 10	U/L
TNF- α	0-87	ng/mL
IL-8	< 5	ng/mL
IL-6	< 7	ng/mL
AST	< 31	U/L
ALT	< 31	U/L
γ GT	9-38	U/L
OCT	8-20	U/L
ALP	< 448	U/L
CRP	< 5	mg/dL
Glucose	3.3-6.1	mmol/L
Ammonia	10-70	mcmol/L

TNF- α , tumor necrosis factor alpha; IL-8, interleukin 8; IL-6, interleukin 6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ GT, gamma-glutamyl transferase; OCT, ornithine carbamoyltransferase; ALP, alkaline phosphatase; CRP, C-reactive protein.

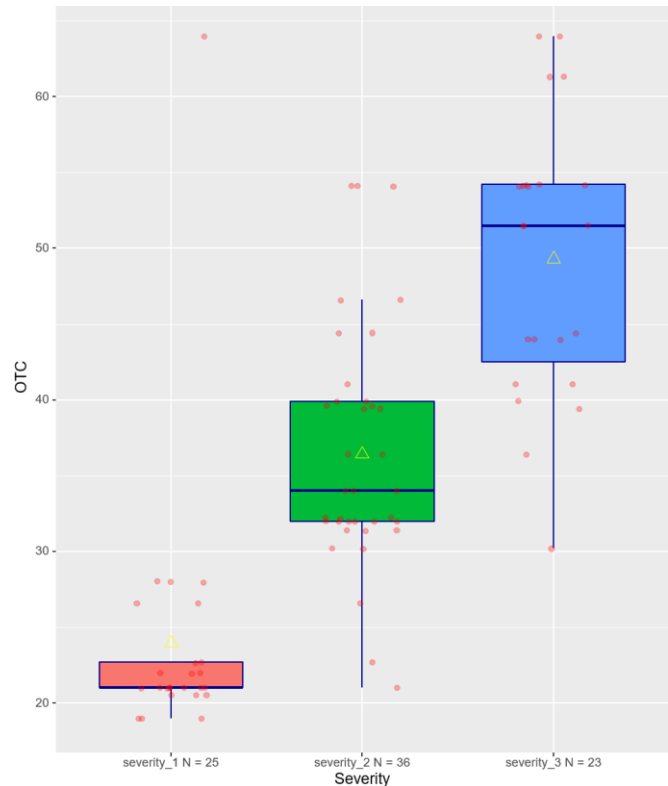
(44.0%), nausea and/or vomiting 68 (80.9%), rapid loss of energy and fatigue 63 (75.0%); hepatomegaly: the liver was enlarged from under the costal arch to 2 cm in 26 (31.0%) and more than 2 cm in 18 (21.4%) patients; ultrasound image detected changes in the structure of hepatic tissue in 31 (36.9%) patients. AST was increased in 35 (41.7%) and ALT in 13 (15.5%) patients. Serum activity of alkaline phosphatase (ALP) was increased in 30 (37.5%), γ GT in 18 (21.4%), and conjugated bilirubin in 15 (17.9%) patients. OCT was increased in 79 (94%) patients: among them 32 (38.1%) with minimally, 40 (47.6%) with moderately, and 7 (8.33%) with significantly increased activity. Hypoalbuminemia was reported in 12 (14.3%) patients. PhL were increased in 15 (17.9%) and β -lipoproteins in 52 (61.9%) patients. Hypoglycemia (mmol/L) was present in 24 (28.6%) patients. LP was increased in all patients 84 (100.0%). Hypercytokinemia test showed increase of TNF- α in 9 (10.7%), IL6 in 55 (65.4%), IL-8 in 69 (82.1%) patients. Hyperammonemia was reported in 29 (34.5%) patients.

The mean level LP of all patients was 3.43 (\pm 0.97), PhL 3.69 (\pm 1.18), TNF α 48.80 (\pm 19.70), IL-8 26.53 (\pm 21.10), IL-6 19.01 (\pm 8.14), AST 32.08 (\pm 12.12), ALT 16.90 (\pm 8.24), γ GT 23.58 (\pm 21.69), OCT 36.25 (\pm 12.81), ALP 506.85 (\pm 269.27), C-reactive protein (CRP) 67.58 (\pm 7.22), glucose 4.51 (\pm 0.55), NH₃ 79.86 (\pm 17.70) respectively.

Comparative analysis by severity groups

Variance analysis by severity groups showed that PhL (p = 0.05), Glucose (p = 0.01), TNF- α (p = 0.01), IL-8 (p < 0.001), AST (p < 0.001), OCT (p < 0.001),

Figure 1. Relationships between serum activity OCT and disease severity.



Y axis- OCT (U/L); X axis- Groups by severity (Severity 1 N = 25, Severity 2 N = 36, Severity 3 N = 23).

ALP (p < 0.001), NH₃ (p < 0.001) have influence on the disease severity. The results of comparison in 3 groups defined by severity for all blood chemistry variables are presented in the Table 2.

Table 2. Variance analysis by severity groups in study patients.

Chemistry Variables	Groups of severity levels of the underlying disease			p-value
	Group 1 (mild) (N = 25) Mean (\pm SD)	Group 2 (moderate) (N = 36) Mean (\pm SD)	Group 3 (severe) (N = 23) Mean (\pm SD)	
Lipid peroxides (g/L)	3.38 (\pm 0.87)	3.39 (\pm 1.00)	3.56 (\pm 1.05)	0.77
Phospholipids (U/L)	3.79 (\pm 1.54)	3.36 (\pm 0.99)	4.10 (\pm 0.86)	0.05
TNF- α (ng/mL)	57.00 (\pm 23.81)	42.29 (\pm 12.76)	50.09 (\pm 20.96)	0.01
IL-8 (ng/mL)	10.80 (\pm 9.66)	28.48 (\pm 18.82)	40.55 (\pm 22.82)	< 0.001
IL-6 (ng/mL)	15.85 (\pm 1.95)	20.15 (\pm 10.01)	20.67 (\pm 8.36)	0.09
AST (U/L)	26.43 (\pm 9.55)	32.88 (\pm 12.87)	36.97 (\pm 11.37)	< 0.001
ALT (U/L)	17.18 (\pm 7.03)	18.24 (\pm 10.25)	14.49 (\pm 5.09)	0.69
γ GT (U/L)	27.69 (\pm 26.66)	23.64 (\pm 21.69)	19.00 (\pm 14.52)	0.29
OCT (U/L)	23.96 (\pm 8.80)	36.43 (\pm 7.96)	49.32 (\pm 9.14)	< 0.001
ALP (U/L)	339.16 (\pm 112.63)	507.11 (\pm 261.91)	688.74 (\pm 289.88)	< 0.001
CRP (mg/dL)	67.61 (\pm 5.94)	66.59 (\pm 7.60)	69.09 (\pm 7.88)	0.57
Glucose (mmol/L)	4.18 (\pm 0.60)	4.69 (\pm 0.52)	4.60 (\pm 0.35)	0.01
Ammonia (mcmol/L)	68.51 (\pm 8.72)	80.51 (\pm 16.84)	91.18 (\pm 19.15)	< 0.001

TNF- α , tumor necrosis factor alpha; IL-8, interleukin 8; IL-6, interleukin 6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ GT, gamma-glutamyl transferase; OCT, ornithine carbamoyltransferase; ALP, alkaline phosphatase; CRP, C-reactive protein.

Regression analysis revealed that the serum activity of OCT (p value < 0.001, OR = 1.27) and NH₃ (p value 0.002, OR = 1.1) significantly predicts the severity of the disease (see Table 3). The difference of serum OCT activity levels in three groups illustrated in Figure 1 using the box plots.

We also performed bivariate correlation analysis and identified that some variables correlate in the following way: TNF-α and OCT (r = -0.3; p value = 0.012); IL-8 and OCT (r = 0.6; p value < 0.001); AST and OCT (r = 0.4; p value < 0.001); γGT and OCT (r = 0.3; p value = 0.014); ALP and OCT (r = 0.6; p value < 0.001); glucose and OCT (r = 0.3; p value = 0.016); NH₃ and OCT (r = 0.4; p value < 0.001).

Discussion

More cases of ARI with hepatic manifestations were detected via OCT than other markers of hepatic injury used in this study. According to our knowledge this is the first study of liver assessment via OCT in pediatric patients with ARI. In the present study, the level of OCT activity was increased in 94% of patients versus other tests of liver injury (AST in 41.7%, ALT in 15.5%, etc). This indicates that liver involvement is better reflected via OCT, than routine tests of hepatic panel.

There are a number of investigations related to liver damage secondary to systemic infections and non-infectious extrahepatic diseases [1–16]. Studies which describe liver involvement in ARI were based on widely accepted methods to characterize liver damage like screening of ALT, AST, ALP, bilirubin, prothrombin time and albumins through blood chemistry, but they are not enough for early and reliable evaluation of liver injury [1-16]. In comparison, AST and ALT are not purely liver-specific, considering their prevalence in a variety of other organs such as heart, muscle, and kidney, while OCT is highly liver-specific and is a

relatively abundant protein [17-27]. Some studies have demonstrated minor degree of hepatocyte damage can lead to early detectable elevation of OCT in blood [18].

It has already been reported that mitochondrion-derived markers such as OCT appeared to be superior to cytosol-derived markers in the detection of liver injury [17-27]. It can identify the degree of hepatic cytolysis and further suggest it as the non-invasive marker for early identification of liver damage. OCT is a principal enzyme in urea cycle catalyzing the reaction of ornithine with carbamoyl phosphate to form citrulline. It is a cell sap enzyme present in mitochondria. OCT can be characterized as a truly liver specific enzyme and a minor degree of hepatocyte damage could create immediately detectable elevation of it in blood [18,19]. The detection of serum levels of OCT plays a valuable role in the diagnosis of liver diseases. It usually reaches up to 100 times the upper limit of its norm during the acute hepatitis [19]. Einheber *et al.* used measurements of OCT as an index of liver damage in acute *P. berghei* infections in mice produced by intraperitoneal infection of parasitized erythrocytes and found serum levels of OCT elevated to five times above those of control mice on fifth and sixth day of infection, indicating liver cell damage [20]. Murayama *et al.* showed the usefulness of OCT for evaluation in acute and chronic liver injuries [21,22].

Our study also suggests that pediatric patients with ARI and with higher serum OCT levels have 27% more chance to experience increased disease severity, which can affect on liver state and prolong hospitalization time and cost. The robustness of our hypothesis can be supported by strong positive correlation between OCT and TNF-α, IL-8, AST, ALP and γ-GT. In other studies, with involvement of 265 Hepatitis C patients the strong correlation was found between OCT and AST, ALT, γ-GT, ALP and other chemokines levels, but relationships between OCT and TNF-α, IL-8 were not significant.

Table 3. Analysis of maximum likelihood estimates (regression analysis).

Parameter	DF	Estimate	Standard error	Wald Chi-square	P > χ ²
Intercept group 3	1	-17.6576	3.7281	22.4333	< 0.0001
Intercept group 2	1	-12.7800	3.2504	15.4595	< 0.0001
Glucose	1	0.2335	0.5569	0.1758	0.6750
Phospholipids	1	-0.4892	0.3370	2.1077	0.1466
TNF _α	1	0.0172	0.0181	0.9025	0.3421
IL ₈	1	0.00334	0.0202	0.0272	0.8691
AST	1	0.0376	0.0272	1.9105	0.1669
OCT	1	0.2352	0.0531	19.6060	< 0.0001*
ALP	1	-0.00071	0.00143	0.2473	0.6190
Ammonia	1	0.0718	0.0233	9.5123	0.0020

* Highly significant difference; TNF-α, tumor necrosis factor alpha; IL-8, interleukin 8; AST, aspartate aminotransferase; OCT, ornithine carbamoyltransferase; ALP, alkaline phosphatase.

However, the final conclusion also states that the measurement of serum OCT concentration may provide a useful marker of the disease severity [23,24].

One of the study limitations was the absence of follow-up examinations. However, in the future it is planned to conduct the similar study with follow-up assessment and in multiple centers to support validity of studies on OCT as a sensitive marker of liver involvement in some extrahepatic diseases.

Conclusion

Liver testing needs to be interpreted in the light of both hepatic, and extrahepatic conditions. Using more sensitive and specific marker of liver damage can detect more cases of ARI with hepatic manifestations. The study also demonstrated a strong correlation between the OCT levels and the severity of underlying ARI in pediatric patients. Pediatric patients with ARI and with higher serum OCT levels have 27% more chance to experience increased disease severity, which can affect on liver state and prolong hospitalization time and cost. The promotion of OCT as a more sensitive and specific marker for evaluation of liver involvement in extrahepatic diseases is an important step forward for replacing several tests by the unique test that will be more cost-effective diagnostic strategy for future patients. We recommend additional large-scale studies of different age groups for OCT informativeness and utilization in estimation of liver injury in various extrahepatic diseases.

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Authors' Contributions

Study concept and design: Vahe Azatyan, acquisition of data: Vahe Azatyan, Lazar Yessayan, Melanya Shmavonyan; analysis and interpretation of data: Vahe Azatyan, Gayane Melik-Andreasyan, Anush Perikhyanyan, Kristina Porksheyanyan.

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