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Role of routine laboratory markers in the diagnosis of rotavirus and adenovirus gastroenteritis

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Abstract

Purpose: The present study aimed to evaluate and estimate the additional and auxiliary diagnostic value of routine laboratory parameters in patients with acute diarrhea caused by rotavirus and adenovirus.

Methods/ patients: A total of 6784 patients diagnosed with acute gastroenteritis were evaluated. Rotavirus and adenovirus infection was diagnosed via a Qualitative immunochromatographic combo rapid cassette antigen test. Complete blood count and biochemical blood tests were performed in all the patients and were compared between the groups according to the positivity or negativity of the virus.

Results: Rotavirus diarrhea was diagnosed in 16.8% and adenovirus diarrhea in 3.2% of patients. Hemoglobin, hematocrit, and mean cell volume (MCV) levels were lower, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were significantly higher in rotavirus positive cases. Neutrophil to lymphocyte ratio was significantly higher, and lymphocyte to monocyte ratio was significantly lower in positive rotavirus cases than negative ones 2.96 and 2.56, respectively ($p<0.001$).

Conclusions: Hematological and biochemical parameters may assist in diagnosing and distinguishing rotaviral and adenoviral gastroenteritis, especially in low-resource environments.

Keywords: adenovirus; children; diarrhea; laboratory markers; rotavirus

Introduction

Pediatric diarrhea is the second leading cause of mortality worldwide among children younger than five years, with an estimated 2 million deaths annually [1]. Even though some countries have adopted the universal use of rota and adenovirus vaccination, there are still nominal immunization rates against viral gastroenteritis in most resource-limited countries. As a result, infection contagion is the most common cause of acute pediatric diarrhea in resource-limited countries. While most common microbial causes of the infectious diarrhea differ by age and geographic region, rotavirus and adenoviruses are the leading pathogens among children under two years of age [2].

The typical clinical features of both pathogens do not differ; both cause vomiting, fever, and non-bloody diarrhea. In severe cases, dehydration, seizures, and even death can occur [3]. In most mild to moderate cases with acute diarrhea, laboratory tests are not warranted. In complicated patients with seizures or altered consciousness, children with suspected

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pneumonia, sepsis, meningitis, or urinary tract infection, relevant investigations are performed. Microbiological evaluation is often required for patients with bloody invasive diarrhea. Laboratory investigations may be used in cases of suspected metabolic acidosis, electrolyte depletion, and severe lactose intolerance. Typical findings are increased blood urea nitrogen, metabolic acidosis, hypokalemia, and dehydration [4, 5].

A general consideration is that blood markers are not valuable for diarrhea management; therefore, few studies in the literature evaluate the role of hematological and biochemical parameters in viral gastroenteritis. Thus, the objective of the current study was to assess and compare the changes in hematological and biochemical parameters related to acute gastroenteritis.

Materials/ patients and methods

Subjects

This retrospective survey was conducted in Düzce University Faculty of Medicine, Outpatient Clinic Department of Pediatrics between January 2015 and October 2019. We included in the study the patients diagnosed with rotavirus positive acute gastroenteritis (RPAG), adenovirus positive acute gastroenteritis (APAG), rotavirus negative acute gastroenteritis (RNAG), and adenovirus negative acute gastroenteritis (ANAG).

In the period, a total of 15119 patients with a diagnosis of gastroenteritis were admitted to our outpatient clinic. Patients with co-infections, pneumonia, inflammatory diseases, upper respiratory tract infection, chronic disease, malignancy, malabsorption syndromes, immunodeficiency, urinary tract infection, malnutrition, and those using any type of medication were excluded from the study. Again, patients with severe clinical course and those who needed intensive care unit admission were also excluded. In the final analyses of the study, a total of 6784 pediatric patients were included.

Ethical approval was obtained from the Clinical Research Ethics Review Committee of Düzce University, School of Medicine (Numbered: 2019/271, Date 16.12.2019). Furthermore, the study was conducted according to principles of the Helsinki Declaration and Good Clinical Practice guidelines. All the participants signed interventional consent form on their admission.

Blood and stool samples

According to the previous data obtained from patients' records: samples were taken into Vacuette blood collection tubes for complete blood count (CBC) and biochemical studies. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, urea, sodium, potassium, chloride, and C-reactive protein (CRP) levels were studied in all of the patients. We also calculated and recorded the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR).

Qualitative immunochromatographic combo rapid cassette test (Xiamen Boson Biotech, China) kit was used for rotavirus and adenovirus detection.

We compared laboratory parameters between the rotavirus and adenovirus groups (RPAG vs. RNAG and APAG vs. ANAG) and investigated the associations, if any, among laboratory parameters.

Analyses

All data were transferred to SPSS v21 (SPSS Inc., Chicago, IL, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Data were given as mean, standard deviation, for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. The Mann-Whitney U test and student's t-test were used for the comparison of quantitative parameters between groups. Comparisons of categorical variables were performed with chi-square tests. P-values lower than 0.05 were accepted to show statistical significance.

Results

Demographic features

We included 6784 children in our study; mean age was 3 (±1.3) years in RNAG, 2 (±1.0) years in RPAG, 3 (±1.0) years in ANAG, and 3 (±1.3) years in APAG. The study population comprised 2915 (43.0%) girls and 3869 (57%) boys.

One thousand one hundred thirty-seven children (16.8%) were diagnosed with RPAG, 217 children (3.2%) were diagnosed with APAG. Age was found to be significantly lower in both RPAG and APAG patients compared to their respective negative groups ($p<0.001$ and $p=0.015$, respectively).

Comparison data for rotavirus evaluation

White blood cell (WBC), lymphocyte, eosinophil, hemoglobin, hematocrit, mean corpuscular volüme (MCV), and platelet distribution width (PDW) levels were significantly lower in patients with RPAG than patients with RNAG ($p<0.001$, for all parameters). Neutrophil to lymphocyte ratio and PLR were significantly higher, and LMR was significantly lower in patients with RPAG than patients with RNAG ($p<0.001$ for all). ALT and AST levels were significantly higher in patients with RPAG than patients with RNAG ($p<0.001$ for both). The mean CRP

levels were not statistically different in RPAG patients and negative patients (p=0.866). Mean platelet volume (MPV) levels showed no difference between RPAG and RNAG patients (7.6 (7.1-8.3) fL vs. 7.7 (7.1-8.3) fL, p=0.208). Demographic, clinical, and laboratory results of the RPAG and RNAG groups are shown in Table 1.

Table 1: Patients' features according to adenovirus evaluation.

	Rotavirus			
	Negative (n=5647)	*Positive (n=1137)*	*Total (n=6784)*	*p*
Age	*3 (1 - 7)*	*2 (1 - 4)*	*3 (1 - 7)*	*<0.001*
Gender				
Girl	2428 (43.00%)	487 (42.83%)	2915 (42.97%)	0.919
Boy	3219 (57.00%)	650 (57.17%)	3869 (57.03%)	
Stay in hospital (hours)	208 (3.68%)	50 (4.40%)	258 (3.80%)	0.251
WBC (x1000)	10.7 (8.2 - 14.1)	9.9 (7.6 - 12.94)	10.5 (8.04 - 13.9)	<0.001
Neutrophile (x1000)	5.99 (3.57 - 9.7)	6.16 (3.9 - 8.9)	6 (3.6 - 9.6)	0.669
Lymphocyte (x1000)	2.8 (1.65 - 4.5)	2.12 (1.24 - 3.51)	2.64 (1.56 - 4.33)	<0.001
Monocyte (x1000)	0.8 (0.57 - 1.11)	0.84 (0.60 - 1.19)	0.80 (0.58 - 1.12)	0.003
Eosinophile (x1000)	0.1 (0.02 - 0.21)	0.02 (0 - 0.1)	0.09 (0.01 - 0.20)	<0.001
Neu / Lym Ratio	2.10 (0.96 - 5.03)	2.96 (1.33 - 6.44)	2.23 (1.00 - 5.22)	<0.001
Plt / Lym Ratio	115.61 (74.82 - 187.45)	156.00 (93.82 - 257.12)	120.74 (77.31 - 198.33)	<0.001
Lym / Monocyte Ratio	3.53 (2.24 - 5.39)	2.56 (1.58 - 3.98)	3.35 (2.09 - 5.20)	<0.001
Hemoglobin (g/dl)	12.30 ± 1.53	12.15 ± 1.26	12.28 ± 1.48	<0.001
Hematocrit (%)	36.80 ± 4.55	36.34 ± 3.59	36.73 ± 4.40	<0.001
MCV (fl)	77.75 ± 6.79	75.64 ± 5.88	77.40 ± 6.69	<0.001
RDW (%)	14.1 (13.3 - 15.2)	14.3 (13.5 - 15.4)	14.1 (13.3 - 15.2)	<0.001
Platelet (x1000)	323 (263 - 399)	321 (269 - 390)	323 (264.5 - 397)	0.742
MPV (fl)	7.7 (7.1 - 8.3)	7.6 (7.1 - 8.3)	7.6 (7.1 - 8.3)	0.208
PCT (%)	0.249 (0.206 - 0.301)	0.246 (0.206 - 0.298)	0.248 (0.206 - 0.301)	0.483
PDW (%)	16.3 (16.0 - 16.7)	16.2 (15.9 - 16.7)	16.3 (16 - 16.7)	<0.001
Urea (mg/dl)	23.95 ± 10.07	28.75 ± 10.60	24.77 ± 10.32	<0.001
Creatinine (mg/dl)	0.36 (0.29 - 0.47)	0.36 (0.29 - 0.43)	0.36 (0.29 - 0.46)	0.070
ALT (IU/L)	16.9 (13 - 23.21)	23.2 (17.8 - 31.78)	17.8 (13.49 - 24.9)	<0.001
AST (IU/L)	34.9 (28.08 - 43.5)	44.5 (36.25 - 53.9)	36.32 (29 - 45.64)	<0.001
CRP (mg/dl)	0.534 (0.2 - 1.86)	0.546 (0.238 - 1.470)	0.536 (0.205 - 1.810)	0.866

Data are given as mean ± standard deviation or median (1st - 3rd quartiles) for continuous variables according to normality and frequency (percentage) for categorical variables

Comparison data for adenovirus evaluation

Lymphocyte count, monocyte count, platelet count, and PCT mean±SD levels were significantly higher in patients with APAG than patients with ANAG. (p<0.001, p=0.024, p=0.019, p=0.021, respectively). Mean CRP levels were lower in APAG patients than in negative patients (p<0.001). There was no statistically significant difference between APAG and ANAG patients in terms of MPV (7.6 (7.1-8.3) fL vs. 7.7 (7.1-8.3) fL, p=0.789). Demographic, clinical, and laboratory results of the APAG and ANAG patients are depicted in Table 2.

Table 2: Patients' features according to adenovirus evaluation.

	Adenovirus			
	Negative (n=6567)	*Positive (n=217)*	*Total (n=6784)*	*p*
Age	*3 (1 - 7)*	*3 (1 - 5)*	*3 (1 - 7)*	*0.015*
Gender				
Girl	2828 (43.06%)	87 (40.09%)	2915 (42.97%)	0.384
Boy	3739 (56.94%)	130 (59.91%)	3869 (57.03%)	
Stay in hospital (hours)	253 (3.85%)	5 (2.30%)	258 (3.80%)	0.241
WBC (x1000)	10.5 (8 - 14)	10.4 (8.43 - 12.9)	10.5 (8.04 - 13.9)	0.639
Neutrophile (x1000)	6.05 (3.61 - 9.64)	5.19 (3.58 - 7.88)	6 (3.6 - 9.6)	0.007
Lymphocyte (x1000)	2.6 (1.54 - 4.3)	3.42 (2.31 - 4.87)	2.64 (1.56 - 4.33)	<0.001
Monocyte (x1000)	0.8 (0.57 - 1.12)	0.86 (0.64 - 1.18)	0.80 (0.58 - 1.12)	0.024
Eosinophile (x1000)	0.09 (0.01 - 0.2)	0.1 (0.03 - 0.2)	0.09 (0.01 - 0.20)	0.154
Neu / Lym Ratio	2.26 (1.02 - 5.31)	1.54 (0.84 - 2.97)	2.23 (1.00 - 5.22)	<0.001
Plt / Lym Ratio	121.88 (77.72 - 200.00)	101.48 (68.61 - 143.22)	120.74 (77.31 - 198.33)	<0.001
Lym / Monocyte Ratio	3.33 (2.07 - 5.19)	3.88 (2.80 - 5.52)	3.35 (2.09 - 5.20)	<0.001
Hemoglobin (g/dl)	12.28 ± 1.49	12.20 ± 1.35	12.28 ± 1.48	0.385
Hematocrit (%)	36.74 ± 4.41	36.29 ± 4.15	36.73 ± 4.40	0.138
MCV (fl)	77.45 ± 6.71	75.98 ± 5.75	77.40 ± 6.69	0.001
RDW (%)	14.1 (13.3 - 15.2)	14.1 (13.3 - 14.9)	14.1 (13.3 - 15.2)	0.380
Platelet (x1000)	322 (263 - 397)	339 (289 - 400)	323 (264.5 - 397)	0.019
MPV (fl)	7.7 (7.1 - 8.3)	7.6 (7.1 - 8.3)	7.6 (7.1 - 8.3)	0.789
PCT (%)	0.248 (0.205 - 0.301)	0.256 (0.226 - 0.3)	0.248 (0.206 - 0.301)	0.021
PDW (%)	16.3 (16 - 16.7)	16.2 (15.8 - 16.5)	16.3 (16 - 16.7)	0.001
Urea (mg/dl)	24.79 ± 10.32	24.10 ± 10.25	24.77 ± 10.32	0.342
Creatinine (mg/dl)	0.36 (0.29 - 0.47)	0.34 (0.3 - 0.42)	0.36 (0.29 - 0.46)	0.012
ALT (IU/L)	17.8 (13.47 - 25)	17.02 (13.58 - 22.27)	17.8 (13.49 - 24.9)	0.127
AST (IU/L)	36.37 (28.92 - 45.8)	36.1 (30.46 - 41.8)	36.32 (29 - 45.64)	0.714
CRP (mg/dl)	0.551 (0.207 - 1.85)	0.297 (0.186 - 0.639)	0.536 (0.205 - 1.810)	<0.001

Data are given as mean ± standard deviation or median (1st - 3rd quartiles) for continuous variables according to normality and frequency (percentage) for categorical variables

Discussion

Rotavirus and adenovirus gastroenteritis epidemiology has a slightly wide range of affected ages (6-8). Both types of gastroenteritis are common between 6-24 months. Rotavirus infection peaks around 9-12 months of age, and adenovirus may be frequently diagnosed up to 5 years of age (8). Rotaviruses are responsible for up to 70% of gastroenteritis among children, and adenoviruses are responsible for the other 30% (9, 10). In our study, the mean age of children positively diagnosed with rotavirus and adenovirus were 2 and 3 years, respectively. The prevalence of rotavirus and adenovirus infection among all the gastroenteritis-diagnosed children in our study was 16.8% and 3.2%, respectively.

The number of white blood cells in the peripheral blood is usually normal in uncomplicated cases. This may help to distinguish rotavirus infection from some

bacterial causes. Specifically, the most common cause of childhood infectious leucopenia is of viral origin and is also frequently shown in bacterial gastroenteritis [11]. In adult patients, we know that lymphopenia is a predictor of bacterial infections, and both lymphocyte and neutrophil count should be considered adult bacteremia. While the ratio of lymphocytes, which play a critical role in destroying viruses, is expected to increase in most viral infections, the opposite is also observed. Monocytes are also considered an indicator of systemic inflammation. The lymphocyte/monocyte ratio represents a better balance between lymphocytes and monocytes [11, 12]. Rotavirus (but not adenovirus-positive) cases presented with lymphopenia in our study. Some studies have evaluated the changes in LMR and NLR in rotavirus gastroenteritis [11, 12]. Consistent with our study, Chi Zhang et al. reported that decreased LMR and increased NLR are significantly observed in children with acute RPAG, and also suggested to utilize these ratio as auxiliary diagnostic markers [13]. With the present study we suggest that together with the clinical outcomes the decreased LMR and increased NLR may be a helpful marker in diagnosing acute rotavirus gastroenteritis, especially in low-resource environments, and thence prevent unnecessary antiviral and antibiotic prescriptions.

The other potential valid parameters to distinguish Rotavirus positive cases from negative ones were hemoglobin, hematocrit, and MCV parameters; in our study, they were significantly lower in RPAG than in RNAG. Previous studies have also reported a slight drop in hemoglobin levels in mild viral infections that may result from virus-associated bone marrow suppression [10, 12].

A slight increase in serum AST levels may be observed during acute illness without further signs of liver damage, indicating damage to intestinal epithelial cells in 15% of the cases [4]. In addition, mild to moderate increase in AST, ALT levels have been reported in some previous studies: some report volumetric increase and no significant difference between rotavirus positive cases compared to negative ones, and other studies report an evident significantly different increase in AST, ALT level in RPAG cases, indicating mild to moderate rotavirus-associated hepatitis [14-16]. Our study partially supports the literature: while the AST and ALT level was in the reference range, the values were significantly higher in the RPAG group.

Inflammatory markers such as CRP, procalcitonin or fecal lactoferrin, and fecal calprotectin may suggest inflammatory rather than viral causes of diarrhea. So generally, these markers are not recommended in acute gastroenteritis because they play no role in diagnostic approach or treatment [17, 18]. Our study supports the literature on the subject that CRP has no diagnostical or distinguishing value in acute viral gastroenteritis cases: the CRP levels were lower in APAG patients and were not statistically different in RPAG patients compared to the negative ones. Although many studies know that CRP level is a pro-inflammatory marker in many viral infections, it is also known that CRP levels can vary depending on age and clinical course [11].

According to some studies, platelets are activated by various factors, and the MPV acts as a negative acute-phase reactant in rotavirus-infected pediatric patients [19, 20]. In our study, mean PDW was lower in RPAG and APAG cases. However, MPV shows no meaningful difference between the positive and negative rotavirus and adenovirus gastroenteritis. Therefore, we do not suggest the MPV value as either a positive or negative acute phase reactant in viral gastroenteric cases.

The most powerful side of our study is that it is a comprehensive study with extensive study data. With this data, we expect to make a valuable contribution to the literature on diagnosis and distinct viral gastroenteritis, and rotavirus and adenovirus positivity as well. However, the weakness of our study is that we have no control group. Further prospective studies with long-term follow-up analyzes would straighten knowledge in this research.

Conclusion

The most remarkable outcomes of our study are as follow. We found that WBC and lymphocyte levels get lower in RPAG compared with the negative ones, AST and ALT levels get higher in RPAG compared with the negative ones; it may have an exhilarative value in Rotavirus diarrhea diagnosis. While MPV and CRP values present no diagnostic change in RPAG compared with the negative cases. On the contrary, CRP levels have a meaningful and clinical increase, while lymphocyte levels significantly and clinically increase APAG. MPV levels have no diagnostic value in APAG either.

Conflict of interest

Authors declare no conflicts of interests

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